Patent
Attorney's Docket No. 000951-089

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#36

In re Patent Application of	
Joseph B. PHIPPS	Group Art Unit: 3734
Serial No.: 08/463,904	Examiner: M. Bockelman
Filed: June 5, 1995	Confirmation No.: 9244
For: METHOD AND DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL	

7-10

BRIEF ON APPEAL

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TABLE OF AUTHORITIES

I. INTRODUCTION

This is an appeal under 37 C.F.R. §1.191 of the final rejection set forth in the Official Action dated June 19, 2002. This Appeal Brief is in compliance with the format stated in 37 C.F.R. §1.192 and the two additional copies of the Brief and the required Official Fee under 37 C.F.R. §1.17(c) have also been provided herewith.

II. REAL PARTY IN INTEREST

The real party in interest is the assignee of the present application, Alza Corporation which is a member of the Johnson & Johnson family of companies.

III. RELATED APPEALS AND INTERFERENCES

Based on present knowledge there are no related appeals or interferences that will directly affect or be directly affected by or have a bearing on the decision by the Board of Patent Appeals and Interferences concerning the instant appeal.

IV. STATUS OF THE CLAIMS

Claims 1, 4 and 7-9 are presently on appeal and all of the claims have been rejected over certain prior art documents. Claims 2, 3, 5, 6, 11, 12, 14 and 15 were canceled without prejudice or disclaimer in an Amendment filed on August 3, 1998, and claims 10, 13, 16 and 17 are being canceled without prejudice or disclaimer in an Amendment Submitted With Appeal Brief concurrently filed herewith. A copy of the claims on appeal is provided in Appendix A.

V. STATUS OF AMENDMENTS

As noted in the previous section, an Amendment Submitted With Appeal Brief is concurrently being filed herewith. Since the Amendment only cancels claims, appellant believes that the Amendment is proper in all respects and should be entered since it reduces the issues on appeal.

VI. SUMMARY OF THE PRESENTLY CLAIMED INVENTION

A. Background

Transdermal drug delivery can be an effective technique for delivering a drug to a patient. Transdermal drug delivery avoids the hepatic first pass effect encountered with oral administration and reduces patient discomfort when compared to subcutaneous injection. In addition, transdermal delivery can provide more uniform concentrations of drug in the bloodstream of a patient over time.[1]

One class of drug that can be administered by transdermal delivery are analgesic drugs that are used for the management of moderate to severe pain. However, the control of these drugs must be carefully monitored in order to provide a sufficient relief from pain while preventing possible overdose.[2] This challenge is particularly significant with the synthetic opiate fentanyl which is about 80 times more potent than morphine. Indeed, due to its opiate character and potency, fentanyl has been the subject of abuse both on the street

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[1] See page 1, lines 11-19.

[2] See page 5, lines 21-25.

and by health care professionals (see the articles provided in Appendix B).[3] One of these articles discusses the problems presented by the abuse of previously worn fentanyl patches.

The dangers of residual fentanyl in used devices is also mentioned in U.S. Patent No. 4,588,580.[4] While this patent only relates to passive transdermal admininstration of fentanyl, which is substantially different from iontophoretic administration as discussed below, the patent specifically cautions in the passage beginning at column 1, line 47:

> Fentanyl and its derivatives are highly potent, rapidly metabolized drugs having a relatively narrow therapeutic index which produce extremely undesirable side effects on overdosage, most notably respiratory depression, which if left unchecked can cause death. They are also relatively expensive and have a high potential for abuse. We have found that these characteristics impose numerous and sometimes conflicting design constraints on a practical transdermal delivery device. For example, **it would be desirable that the device deliver the drug at a substantially constant rate for at least about 24 hours while at the same time keeping the amount of drug within both the unused and depleted systems to a minimum.** (emphasis added)

The potential for abuse is also reflected in the Merck Index which includes the statement: "Caution: Abuse leads to habituation or addiction."[5] A more recent illustration of the potency and danger of fentanyl is the incident involving the seizing of a crowded Moscow theater in October, 2002, by Chechen separatists. Russian forces introduced a gas containing a form of fentanyl into the theater which resulted in the deaths of over 100 hostages in the theater.[6]

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[3] The articles are from the American Journal of Health-System of Pharmacists and the Journal of Forensic Sciences that were provided with the response dated August 3, 1998, and which refer to a number of other articles published in the 1980's and early 1990's.

[4] The '580 patent was referred to by the Examiner in the final Action, but not specifically incorporated in any rejection.

[5] Excerpt from the Tenth Edition of the Merck Index is also provided in Appendix B.

[6] An excerpt from the Washington Post website is further provided in Appendix B. This incident occurred after final Official Action dated June 19, 2002, and the information

In addition to its high potency, fentanyl is characterized by a rapid onset of analgesia (if injected) and short duration of action.[7] When fentanyl is administered with passive transdermal patches, the drug is continuously delivered to the patient with the amount of drug in the patch being determined by the dosage to be administered. One of the drawbacks of passive transdermal patches is that there is a significant lag time required to achieve the desired steady-state plasma levels.[8] Electrotransport delivery devices, which utilize electric current and charged moieties and therefore operate on a different basis than the diffusion of uncharged materials involved with passive transdermal delivery, can significantly reduce the lag time necessary to achieve peak plasma levels and can administer the drug until the donor reservoir is essentially depleted. However, it has been difficult to maintain a predictable transdermal electrotransport flux at a particular applied current level.[9]

B. The Present Invention

The presently claimed invention relates to a method for delivering an analgesic drug selected from the group consisting of fentanyl salts through a body surface by iontophoresis (a type of electrotransport) from a delivery device having a donor reservoir containing an at least partially aqueous solution of a fentanyl salt. As discussed above, by using electric current to power drug administration, iontophoresis can be used to essentially deplete the

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is being provided to further illustrate the understanding in the art of the potentially dangerous nature of fentanyl.

[7] See page 5, line 26 to page 6, line 5.

[8] See page 6. Additionally, since passive transdermal patches rely diffusion, the efficiency of administration decreases as the drug is depleted.

[9] See pages 7-8.

donor reservoir. However, it has been found in accordance with the present invention that by maintaining the concentration of a fentanyl salt in an aqueous solution in the donor reservoir well above depletion, specifically at a level above about 16 mM, the iontophoretic flux can be maintained at an essentially constant level at a constant current substantially throughout the analgesic drug delivery period wherein the analgesic drug is delivered through the body surface. It is important to understand that the defined relatively high concentration of fentanyl salt is maintained during the total delivery period and that accordingly, delivery is terminated long before the contents of the reservoir are depleted.[10]

By following the present invention, one can achieve a high level of predictability since the delivery of the drug is terminated before a significant decrease in the normalized flux occurs. That is, one can select the desired level of flux by selecting the appropriate iontophoretic current. This understanding of the present invention is illustrated in Figure 2 (copy provided in Appendix C) which shows the consistency of normalized flux when the fentanyl HCl concentration is maintained above about 6 mg/ml which corresponds to above about 16 mM. This Figure not only illustrates the importance of the defined concentration, but also shows the relatively precipitous decline in normalized flux when the concentration is below the recited amount.

The prior art of record does not disclose or suggest the present invention and from the preceding discussion, it can further be understood that the present invention maintains a relatively high concentration of fentanyl salt in the donor reservoir substantially throughout the total delivery period and then, contrary to conventional wisdom concerning fentanyl handling, terminates delivery while there is a substantial concentration of fentanyl in the

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[10] See pages 12 and 13 and Example 1.

donor reservoir. It is by following the claimed method, appellant has found that one can attain a predictable essentially constant iontophoretic flux at a constant applied current level throughout the total delivery period.

C. The Declarations Under 37 C.F.R. §1.132 by Dr. Phipps

During the lengthy prosecution of the present application, two Declarations Under 37 C.F.R. § 1.132 were submitted by the inventor, Dr. Joseph B. Phipps, to provide a more clear understanding of the background of the present invention and the distinctions over the prior art.[11] The first Declaration was submitted on June 9, 1997, and explains the reasons why the teachings of the then cited documents would not lead to the invention in order to respond to the Examiner's position concerning the alleged absence of evidence showing that the prior art would not result in the invention. The Declaration also explains the potency of fentanyl and the potential for abuse or misuse.

Provided with the Declaration were two technical literature articles. The first was an article by R. V. Padmanabhan et al entitled "*In Vitro* and *In Vivo* Evaluation of Transdermal Iontophoretic Delivery of Hydromorphone". The article describes experiments involving the iontophoretic delivery of hydromorphone hydrochloride and indicates the delivery rate was independent of the concentration of hydromorphone in the donor solution over the range from 0.01M to 0.8M and states on page 130:

> Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

[11] A copy of each of the Declarations is provided in Appendix D.

The second article was by G.B. Kasting and J.C. Keister and is entitled "Application of Electrodiffusion Theory For A Homogeneous Membrane to Iontophoretic Transport Through Skin". The article makes theoretical predictions of the effect of donor drug concentration drug concentration on drug delivery efficiency (i.e., rate of drug delivery per unit current) for several cases. In Case 1, the theoretical prediction for a drug salt with no added NaCl in the donor reservoir and normal saline on the receptor side of the in a vitro cell is described and the conclusion set forth on page 204 is:

> ...the efficiency of drug delivery is largely determined by the ratio of drug diffusivity in the skin to that of the predominant counterion on the opposite side of the membrane. It is independent of drug concentration in this example.

The second Declaration, submitted on August 3, 1998, provides an explanation of certain teachings of the prior art and further explains the two articles submitted with the first Declaration.

VII. ISSUES ON APPEAL

The first issue on appeal is whether claims 1, 4 and 7-9 are properly rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Phipps et al, U.S. Patent No. 5,423,739 (hereafter the '739 patent), an excerpt from a Russian text by Rebinder, Phipps et al, U.S. Patent No. 5,125,894 (hereafter the '894 patent), and Muller et al, U.S. Patent No. 5,320,731.

A second issue is whether the same claims are properly rejected under 35 U.S.C. §102(b) as being anticipated by Haak et al, U.S. Patent No. 5,203,768, and whether the claims have been properly rejected under 35 U.S.C. §103 as being unpatentable over the

combination of Haak et al in view of Rebinder, the '894 patent and Muller et al or in view of Newman, U.S. Patent No. 4,931,046.

A third issue is whether the claims are properly rejected under 35 U.S.C. §102(b) as being anticipated by the claims of Theeuwes et al, U.S. Patent No. 5,232,438, and whether the claims have been properly rejected under 35 U.S.C. §103 as being unpatentable over the combination of Theeuwes et al in view of Rebinder, the '894 patent and Muller et al or in view of Newman.

A yet further issue is whether the claims have properly been rejected on "obviousness-type" double patenting grounds over the claims of U.S. Patent No. 6,171,294.

VIII. GROUPING OF CLAIMS

The claims do not all stand or fall together for the reasons that will be apparent from the argument set forth with greater precision below. Claim 9 further specifies that the electrotransport flux is substantially proportional to a level of electrotransport current applied by the delivery device during the iontophoretic drug delivery. Based on the description provided in the specification and above and the illustrated effect in Figure 2, the recitation in claim 9 reinforces the distinction over the prior art that the fentanyl delivery from an iontophoretic delivery device should be terminated upon completion of the total delivery period while a substantial amount of fentanyl remains in the donor reservoir.

IX. ARGUMENT

A. The Prior Art Relied on by the Examiner

1. Phipps et al (the '739 Patent)

The '739 patent relates to a device and method for iontophoretic delivery. The device has a two-layer active electrode element which is composed of an overlapping skin contacting hydrogel and carrier layers. The carrier layer contains dispersed or dissolved active agent. The list of possible active agents extends from column 13, line 40 to column 14, line 46. This list includes hundreds of agents, with fentanyl being one, and which reads in its entirety:

> Active agents useful in the present invention include any pharmaceutical compound or chemical that is capable of being ionized or converted to a charged form and would be administered to a host including animals and man for the purpose of obtaining a therapeutic effect. A variety of active agents intended to be introduced into the host may be combined with the carrier layer. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics including fentanyl, sufentanil, buprenorphine and analgesic combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents such as terbutaline, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness preparations such as scopolamine and ondansetron, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary anticholinergics, sympathomimetrics, xanthine derivatives, cardiovascular preparations including calcium channel blockers such as nifedipine, beta-blockers, beta-agonists such as dobutamine and ritodrine, antiarrythmics, antihypertensives such as atenolol, ACE inhibitors such as rinitidine, diuretics, vasodilators, including general, coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones such as parathyroid hormone, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetrics, prostaglandins, proteins, peptides, psychostimulants, sedatives and tranquilizers.
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> The invention is also useful in the controlled delivery of peptides, polypeptides, proteins and other macromolecules. These macromolecular

substances typically have a molecular weight of at least about 300 daltons, and more typically have a molecular weight of at least about 300 to 40,000 daltons. Specific examples of peptides and proteins in this size range include, without limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, napharelin and leuprolide, GHRH, GHRF, insulin, insulotropin, heparin, calcitonin, octreotide, endorphin, TRH, NT-36 (chemical name: N-[[(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG, desmopressin acetate, etc.), follicle luteoids, .alpha.ANF, growth factors such as growth factor releasing factor (GFRF), .beta.MSH, somatostatin, bradykinin, somatotropin, platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin (ACTH), erythropoietin, epoprostenol (platelet aggregation inhibitor), glucagon, hirulog, hyaluronidase, interferon, interleukin-1, interleukin-2, menotropins (urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, desmopressin, ACTH analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists, antidiuretic hormone agonists, bradykinin antagonists, CD4, ceredase, CS1's, enkephalins, FAB fragments, IgE peptide suppressors, IGF-1, neurotrophic factors, colony stimulating factors, parathyroid hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists, pentigetide, protein C, protein S, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines, vasopressin antagonist analogs, alpha-1 anti-trypsin (recombinant), and TGF-beta.

Additional agents include pilocarpine nitrate, lidocaine hydrochloride, hydrocortisone derivatives, sodium salicylate, acetic acid, fluoride anion, lithium, antibiotics such as penicillin and cephalosporin and dexamethasone sodium phosphate, hydromorphone, diazepam salts, antihypertensive agents, bronchodilator agents, peptide hormone and regulatory agents and proteins.

Only hydromorphone hydrochloride and lidocaine hydrochloride are exemplified.

2. Rebinder

Rebinder is a translation of Chapter 12 of a Russian text which chapter is entitled "IONTOPHORESIS". The chapter provides a general description of iontophoresis, but does not specifically relate to the iontophoretic delivery of fentanyl which provides different challenges compared to other drugs for the reasons previously provided. Rebinder describes certain observations based on limited studies that had been conducted up to 1956

(the apparent date of the document cited by the Examiner). Rebinder describes in Section 45 starting on page 10 of the translation which is entitled "Fundamentals of Iontophoresis", various principles and equations and explicitly states on page 12:

> It is important to note that the quantity n_1, and thus, in accordance with equation (253), the amount of substance introduced, is completely governed by the parameters of the internal solution and the skin tissue, and **does not depend on the concentration of the medicinal substance used for iontophoresis.** (emphasis added)

Rebinder describes actual experiments, such as iontophoresis on isolated skin in Section 48 starting on page 21 of the translation. The results are set forth in Table 119 on page 22 of the translation with certain conclusions being provided thereafter including the conclusion which reads:

> 2. The amount of substance introduced is proportional to the amount of electricity, consequently, the transport numbers in the skin do not change in the course of the experiment. This justifies citing the amount introduced per coulomb (p/q); **no dependence of p/q on current strength or duration was detected.** (emphasis added)

A similar conclusion is set forth after another series of experiments reported in Table 120 on page 25 of the specification. The first conclusion after these experimental results reads:

> 1. The amount of substance introduced was found to be directly proportional to the quantity of electricity; **no relationship between p/q and current strength, density, or duration of the experiment was found.** (emphasis added)

The Examiner has stated that Rebinder recognizes the influence of "parasitic ions" and has quoted various passages including the one from pages 30 and 31 of the translation which reads:

> With increasing concentration of solutions (higher than .1M, i.e., 3-4%) of complex organic substances it becomes necessary to take into

consideration the possibility of association complexes forming, i.e., with the transition from a solution of a "colloidal electrolyte," as occurs, for instance dyes. In this case the process of iontophoresis becomes one of electrophoresis, and the amount of substance introduced may increase due to the increase in mass of the ion, since the linear mobility of colloidal particles is usually close to that of organic ions ($=2x10^{-4}$ cm/s). Nor should we forget the possibility of the reverse effect, namely, the decrease in the transport number in the skin as the particle size increases. **The problem of how these effects are inter-related and the question of whether it is possible for association complexes to form in solutions of medicinal substances used for iontophoresis remain unresolved and require further research.** (emphasis added)

3. Phipps et al (the '894 Patent)

The '894 patent relates to a method and apparatus for controlled environment electrotransport, particularly by controlling the ionic environment of the active (donor) electrode reservoir. Control can be achieved by maintaining the pH at a certain level or by maintaining selective control over the delivery rate of a target species. In the passage beginning at column 9, line 65, the '894 patent provides "Some General Observations Regarding Iontophoresis". Included within this passage is the statement at column 10, lines 41-43 which reads:

> In general, the amount of transport which occurs as a result of applied voltage is directly proportional to the amount of current passing through the cell. Thus, in general, if the amount of current is doubled, the rate of transport due to the electromotive force is also doubled.[12]

The '894 patent continues with a description of various factors that can affect the stated general principle including the charge of migrating species, the presence of extraneous ions in the active reservoir and the effect of the concentration of drug ions. In this last respect, the patent at column 11, lines 9-16 again refers to the aforementioned Padmanabhan article and states:

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[12] Citation to the Padmanabhan article discussed above.

In general, although rate of drug delivery is proportional to current, at a constant current the rate of drug delivery (R_d) is independent of drug concentration (i.e., target species concentration) in the active electrode reservoir, provided that the concentration is at least above a threshold level (and little or no extraneous ions are present).

The general and preferred techniques of attaining the desired control of the electrotransport system are described in the passage beginning at the bottom of column 14 to the bottom of column 22. To illustrate the principles, the '894 patent provides a series of experiments wherein hydromorphone is the drug that is delivered. Table 2 at the top of column 37 shows that for hydromorphone hydrochloride, the average steady-state rate is essentially constant for a drug concentration that ranges from 10 to 800 millimolar.

4. Muller et al

Muller et al relates to an iontophoresis device for transcutaneous administration of an active principle to a patient which comprises electrodes, at least one of which is a consumable electrode formed of an electrochemically consumable material associated either with an insulating support or with a particular electronically conducting support. Active principles are identified at column 6, lines 28-34 as being: "insulin, metoprolol, hydrocodone, tetracyclines, salbutamol, valproic acid, propranolol, arginine-desmopressin, despopressin or others. Fentanyl is not mentioned in the patent.

The Examiner has cited Muller et al for the paragraph starting at column 3, line 50 which reads:

If the reservoir element held, at the start of the operation, only a quantity of active principle equal to the given total quantity of active principle to be administered, and if the current was passed until this quantity had entirely diffused through the skin of the subject, the said current, towards the end of the operation, would act above all to transport ions other than those of the active principle, which would lead to excessive energy consumption and long treatment times. It is therefore preferable, in order to avoid the above drawbacks, for the quantity of active principle present in the

reservoir element at the start of the operation to be in excess with respect to the said given total quantity, the said excess being able, for example, to be from approximately 2% to 1000% and more specifically from approximately 2% to 500% of this given total quantity.

5. Haak et al

Haak et al discloses a transdermal drug delivery device which includes both an active drug reservoir (from which drug is delivered by iontophoresis) and a passive drug reservoir (from which drug is delivered by diffusion). The respective drug reservoirs can be electrically insulated from one another or can be contained in the same reservoir. Drugs which can be delivered by the disclosed device are set forth in columns 12 and 13. In Example 1, fentanyl is delivered in an amount of 25 μg/hr by passive delivery and a bolus of 25 μg every 5 minutes can be delivered by iontophoresis for a total delivery rate of 325 μg/hr.

6. Newman

Newman describes an iontophoresis drug delivery system and particularly a table top model as illustrated in Figure 3. In the system, the medication is retained in non-charged form such that it can be electrically charged. Although the patent does not specifically mention fentanyl, it does refer to pain killing drugs in the passage beginning at column 7, line 47 which reads as follows:

> The application of pain killing drugs can also be suitably monitored so as to avoid respiratory failure which may occur if an excessive dosage thereof is given to the patient, thus the patient's heart beat rate can be monitored, as by using well known capacitive sensors for monitoring pulse rates, and supplied to the microprocessor so that if such rate exceeds a selected level during the delivery of a pain killing medication, such delivery can be stopped to avoid drug overdose and the possibility of respiratory arrest. Moreover, the microprocessor can also be arranged so that the delivery of a pain killing medication can be activated by the patient himself or herself (as by pushing a start button). The microprocessor can be further programmed so that the patient cannot start a subsequent delivery until a

selected time period has elapsed from a previous delivery in order to avoid an excessive dosage. Further, the microprocessor can by programmed so that when a patient is in an extremely painful state, the current level used for delivery can be set to an operating level initially which is much higher than would normally be used (e.g. 2 Io)so that a bolus of the medication can be delivered immediately. The current is then subsequently set at a much lower level than the normal operating level so that the remainder of the medication is delivered at a much lower dosage rate thereafter. Thus, a more immediate therapeutic effect is achieved for a patient in pain distress.

7. Theeuwes et al

Theeuwes et al relates to a electrotransport system which includes a membrane capable of controlling the release of agent from an electrotransport agent delivery system where passive delivery is inhibited, but not delivery under an electric current. The Examiner has considered the claims of the patent to be relevant and, as only method claims are currently at issue, claim 13 of Theeuwes et al is reproduced as follows:

13. A method of inducing analgesia, comprising:

placing an electrotransport agent delivery electrode assembly on a body surface, the electrode assembly including a drug reservoir and a means for electrically connecting said drug reservoir to a source of electrical power, the drug reservoir containing an analgesic drug in a form susceptible to electrotransport delivery through the body surface, the drug being selected from the group consisting of fentanyl, sufentanil, analogues of fentanyl, analogues of sufentanil and pharmaceutically acceptable salts thereof;

electrically connecting the drug reservoir to the source of electrical power;

placing the drug reservoir in drug-transmitting relation with the body surface; and

delivering the analgesic drug through the body surface by means of electrotransport, the drug being delivered at a rate sufficient to induce analgesia.

8. Southam et al

Southam et al has been relied on to support the "obviousness-type" double patenting rejection. The nine claims of the patent read as follows:

1. A method of obtaining self-administered analgesia in a human patient who is suffering from pain consisting of transdermally delivering solely by electrotransport a dose of about 20 μg to about 60 μg of fentanyl over a predetermined delivery period of up to about 20 minutes from an electrotransport device which includes a donor reservoir hydrogel formulation comprised of fentanyl, terminating said delivery at the end of said delivery period and allowing the patient to self-administer from about 10 to about 100 additional of said doses over a period of 24 hours.
2. The method of claim 1, wherein about 35 μg to about 45 μg of fentanyl is delivered over a delivery period of about 5 to 15 minutes.

3. The method of claim 1, wherein about 40 μg of fentanyl is delivered over the delivery period.

4. The method of claim 1, wherein the delivery period is about 10 minutes.

5. The method of claim 1, wherein the additional doses are 35 μg to 45 μg doses of fentanyl.

6. The method of claim 1, wherein the donor reservoir formulation comprising a fentanyl salt is placed in contact with the body surface.

7. The method of claim 6, wherein the fentanyl salt comprises about 1.9 to 2.0 wt % of the formulation.

8. The method of claim 7, wherein the fentanyl salt is fentanyl hydrochloride.

9. The method of claim 6, wherein the donor reservoir formulation comprises polyvinyl alcohol.

B. The Examiner's Rationale for the Prior Art and Double Patenting Rejections

In the final rejection dated June 19, 2002, the Examiner set forth an extensive discussion of the various prior art and double patenting rejections, as well as additional arguments. Although the prior art discussion and additional arguments are too lengthy to repeat in their entirety, the Examiner has essentially taken the position that the present invention is no more than an obvious optimization of art recognized parameters or is inherently met by one or more of the cited documents and is not patentably distinct from the

invention claimed in Southam et al. For instance, with respect to the first combination of documents, the Examiner has initially stated:

> While it was long recognized that fentanyl salts as well as hydrogel layers were well known constituents in iontophoretic systems, Phipps '739, like others fail to specify the particulars of the drug concentration as defined in the claimed invention.

In relying on Rebinder, the Examiner stated:

> It is clear as far back as 1956 that the concepts that: 1) for concentrations regarded as normal working concentrations, iontophoresis for simple ions is independent of concentration 2) the relative amount of parasitic ions to major ions effects the delivery rate of simple as well as complex ions 3) the delivery of complex organic ions may involve other factors, and most importantly, 4) **further research to discover the relationship between concentration and drug delivery for the various complex ions is desired.** (original emphasis)

As to Phipps '894, the Examiner stated:

> Phipps '894 dedicates the patent to various types of operation based upon these principles so as to make the drug delivery process more predictable. It's teachings are based upon those principles found in the earlier teachings of Rebinder. It is clear from the Phipps et al '894 disclosure that drug delivery predictability is essential for achieving success and that the determination, use and maintenance of drug concentration levels above a threshold levels for achieving predictability of delivery was well known. It is also apparent that the threshold levels for various drugs will vary from species to species. Therefore to have tested, determined and used the threshold levels for fentanyl and applied them to an known iontophoretic system such as that of Phipps et al '894 whether or not added intentionally added extraneous ions are present would have been an obvious optimization of parameters to those of ordinary skill in the art to sustain desired levels of drug flux.

Muller et al was relied on for its teaching of using excess material based on the quoted passage. The Examiner then concluded:

> Thus, it is apparent that the prior art recognized that it was important to be able to predict the amount of drug delivered per coulombs applied and that one must experiment using the particular drug be delivered to determine its properties. It was also known at the time of applicant's invention that in order to deliver a desired quantity of medicament to a patent [sic], excess

quantities must be provided so as to negate the effects of competing ions since efficiency decreases as drug delivery ions are depleted in the reservoir. It was also recognized that a threshold value exists wherein the effects of competing ions are no longer felt and that the amount of drug delivered become strictly dependent on the amount of current applied. Given these facts as demonstrated in the prior art and taking into consideration that Phipps '739 recognizes that fentanyl may be delivered to the body in aqueous salt forms, it would have been obvious at the time of applicant's claimed invention to use fentanyl in an iontophoresis patch and to perform the routine testing of determining the most safe and effective concentrations of drug in the reservoirs to achieve patient analgesia.

For the second set of rejections, the Examiner took the position that Haak et al inherently met the claims based on the Examiner's interpretation that the disclosed rate of administration of 25μg every 5 minutes must be linear because otherwise the device would deliver less than the stated amount for each subsequent interval. The Examiner's fall back positions relating to the rejection under 35 U.S.C. §103(a) are as follows:

> If not inherent, it would have been obvious in view of the collective teachings of Rebinder, Phipps '894 and Muller et al for reasons explained in the earlier rejection of Phipps et al '739 in view of the combined teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731 to have operated the device in the linear region for fentanyl which would inherently include at least a portion of applicant's claimed range.
>
> Alternatively, it would have been obvious in view of Newman to have placed as much drug as desired into the Theeuwes device and limit the amount delivered by a control circuit so that the patient may undergo self treatment for days on end. Starting at column 7 line 47, Newman describes a system in which pain killing drugs are placed in an iontophoretic system which maybe patient controlled so as to let subsequent deliveries be administered by the patient but prevent overdosages. To have implemented such a system with the Phipps et al device is provided [sic] high concentrations fentanyl so as to provide multiple dosages of pain killing medication would have been obvious.

The alleged anticipation and obviousness rejections based on the third set of documents is relatively succinct and reads as follows:

> The claims of Theeuwes et al USPN 5,232,438 recite a device and a method for inducing analgesia in a patient using fentanyl salt. The examiner

considers the recited concentrations in the applicant's pending claims to be inherent in the Theeuwes et al claims, for had the reservoir contained an concentration less than the requisite 16 mM, the amount actually delivered would have been less than Theeuwes et al calculated and the results of the claimed invention would have not been yielded. Although the specification of Theeuwes provides little information for such a method and device, the examiner still considers it inherent. Alternatively, it would have been apparent to one of ordinary skill in the art, that for such a device and method to be accomplished one would have tested various concentrations of fentanyl salts to achieve the greatest efficiency and safely according to the principles of the collective teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731.

Alternatively, it would have been obvious in view of Newman to have placed as much drug as desired into the Theeuwes device and limit the amount delivered by a control circuit so that the patient may undergo self treatment for days on end.

As for the "obviousness-type" double patenting rejection over the claims of Southam et al, the Examiner stated:

Claims 1, 4, 7-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,171,294. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the current application recites a method of drug delivery where in the concentration is maintained above about 16 mM which from applicant's specification is a composition that comprises about 1-2% fentanyl which is also the same composition as claim 7 of the 6,171,294 patent. Therefore claim 1 of the current application is merely a broader version of claim 1 of the '294 patent with the intended dosaging schemes of claim 1 of the '294 patent deleted.

C. The Combination of The '739 Patent, Rebinder, The '894 Patent, and Muller et al Would Not Result in the Presently Claimed Invention

The proposed combination of prior art does not establish a *prima facie* case of obviousness. The combination uses an improper "obvious to try" standard and relies on appellant's own specification in an attempt to justify the rejection.

As discussed above, the present invention specifically relates to the drug fentanyl and provides a method for administration that provides a beneficial effect of attaining

consistent iontophoretic flux, but which leaves a substantial amount of fentanyl in the donor reservoir after the total delivery period. In view of the fact that fentanyl is a powerful narcotic that has been known to be the subject of misuse and abuse, such as when previously worn devices are used (as noted in the articles provided in Appendix B), those of ordinary skill in the art would be led to a practice of attempting to completely deplete the donor reservoir of fentanyl at the conclusion of the total drug delivery period.

This understanding is supported by the discussion provided in the Kasting et al article that was discussed in the first Declaration by Dr. Phipps. As explained by Dr. Phipps, the article provides theoretical predictions of the effect of donor drug concentration on drug delivery efficiency (i.e., rate of drug delivery per unit current) for several cases. Case 1, beginning on page 202, develops the theoretical prediction for a drug salt with no added NaCl in the donor reservoir and normal saline on the receptor side of the in vitro cell. On page 204, the article concludes that, for this case:

> ...the efficiency of drug delivery is largely determined by the ratio of drug diffusivity in the skin to that of the predominant counterion on the opposite side of the membrane. It is independent of drug concentration in this example.

This understanding in the art is reinforced by the Padmanabhan article which discloses that the flux of hydromorphone is independent of concentration over a broad range extending to a small drug concentration of less than 1 mM which is far below the concentration defined in the claims on appeal.

The '739 patent quite clearly relates to a device and method for iontophoretic drug delivery. Just as clear is the fact that the patent does not specifically relate to fentanyl, does not focus on special treatment of this drug and certainly does not teach the claimed

method with the defined concentration. The Examiner has conceded this last point by stating in the Final Action:

> While it was long recognized that fentanyl salts as well as hydrogel layers were well known constituents in iontophoretic systems, Phipps '739, like others fail to specify the particulars of the drug concentration as defined in the claimed invention.

In an attempt to bridge this conceded shortcoming of the '739 patent, the Examiner has first relied on Rebinder. This 1956 text again relates generally to iontophoresis and does not focus on fentanyl and the challenges this potent narcotic presents. Indeed, from the passages quoted above, the document actually supports the understanding that there is no dependence of the amount of drug introduced on the concentration of drug used for iontophoresis and there is no dependence of the amount introduced per coulomb (p/q) on current strength or duration.

The Examiner has noted that Rebinder recognizes the effect of parasitic ions, but has emphasized his reliance on the document for the proposition that "**further research to discover the relationship between concentration and drug delivery for the various complex ions is desired.**" (original emphasis)

The Examiner's stated reliance on Rebinder for the emphasized general proposition to conduct further research does not satisfy the standard necessary to establish a *prima facie* case of obviousness. Such a conclusion is evident from the decision in *The Gillette Co. v. S. C. Johnson & Son Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990) where the court stated upon upholding the validity of a patent:

> Johnson takes the position that, at most, the substitution suggested by Gillette may be "obvious to try." As we recently explained,
>
> > [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, **such that**

> **further investigation might be done as a result of the disclosure**, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.[13]

The court then set forth the well known conclusion that "obvious to try" is not equated with obviousness under 35 U.S.C. §103. Therefore, given the fact that Rebinder has nothing to do with fentanyl administration, only invites further research and actually provides statements that concentration and duration are generally non-factors, would inevitably lead to the conclusion that the Examiner has improperly relied on this document and, if anything, the document supports, rather than detracts from, the patentability of the present invention.

A word is believed to be in order about the influence of "parasitic ions" which is mentioned in Rebinder and other documents. Essentially, the presence of "parasitic ions" decreases the efficiency of iontophoretic delivery as the concentration of the "parasitic ions" increases. Such an understanding has nothing to do with the present invention. This has been made clear by the discussion provided by the inventor, Dr. Phipps, in his second Declaration wherein he explained:

> While secondary to my primary disagreement with the Examiner on what is obvious and what is not, the Examiner has seemingly failed to appreciate the role of extraneous ions on the threshold concentration concept. This misconception is understandable since many researchers in this field to this day fail to grasp the finer elements of the competing ion effect.
>
> The Examiner incorrectly asserts that; (a) the presence of extraneous ions like Na^+ and K^+ in a formulation diminishes the relevance of the Kasting model cited in my previous Declaration; and, (b) that the reason that a higher threshold is observed for some drugs may be due to the extraneous ion concentrations in the formulation employed.

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[13] Emphasis added and citations omitted at 919 F.2d 725, 16 USPQ2d 1928.

In making these assertions, the Examiner is assuming that the extraneous ions, if present at the beginning of treatment are still present at the end of treatment. In fact, because small excipient ions (like Na^+ and K^+) are much more mobile in the solution and skin than the fentanyl ions and are typically present in an amount less than the amount of the drug ions, they are substantially depleted during the first part of treatment. Therefore the Kasting model is an important and fully appropriate consideration of the state of the art at the time of my invention. Contrary to the Examiner's assertions, the Kasting model teaches away from my invention, even when extraneous ions are initially present, since it predicts in theory that no threshold in concentration should exist, that is, that the flux of drug at constant current should remain essentially constant until the last molecule is delivered.[14]

The Examiner's further reliance on the '894 patent is a further instance of a generalized invitation to conduct experimentation which has been shown to be legally insufficient to support a rejection under 35 U.S.C. §103. The '894 patent does not even mention fentanyl. Quite to the contrary, the '894 patent describes the iontophoretic delivery of hydromorphone and illustrates in Table 2 that even with a drug concentration as low as 10 mM, the average steady state rate is approximately the same as it is at 800 mM. Moreover, in the passage bridging columns 34 and 35, the patent makes the observation that when extraneous ions are present, such as sodium and potassium, they are transported at a faster rate than the hydromorphone which is precisely what was discussed above to explain why extraneous ions are not responsible for the high concentration defined in the claims of record. Thus, the fair teachings in the '894 patent supplement those set forth in the aforementioned Padmanabhan article which again discloses that the flux of

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[14] The discussion at the bottom of page 25 of the application likewise does not contradict or detract from this understanding. It has been explained during the prosecution of the present application that the statement that as the fentanyl HCl concentration falls below 6 mg/ml (about 16 mM), a more significant portion of the electrotransport current is carried by ions other than fentanyl ions refers to the increasing effect of chloride ions which migrate from the other side of the epidermis.

hydromorphone is independent of concentration over a broad range extending to a small drug concentration of less than 1 mM.[15]

As for the Examiner's reliance on the threshold level mentioned in the '894 patent, Dr. Phipps directly address this passage in his Declaration wherein he stated:

> This statement requires no unique knowledge of drug transport and is an entirely obvious concept. That is, since drug flux was known to be independent of drug concentration over some concentration in a range (e.g., as stated in the Padmanabhan article), and since drug flux is obviously zero at zero concentration, then to conclude in the '894 patent that a "threshold value" exists is an obvious concept requiring no unique knowledge about the mechanism of drug transport through the tissue. In addition, the statement in the '894 patent that this threshold value is likely dependent on the physical/chemical properties of the drug species and tissues is also an obvious general principal that is the void of mechanistic or drug-specific knowledge.

What appellant has found that despite the evidence in the art that the threshold level is very low (down to 1 mM for hydromorphone) and despite the caveats in the art which warn about the potential misuse of narcotics (including used devices), thus reinforcing the use of low residual concentrations, fentanyl requires a high concentration in order to maintain a relatively constant iontophoretic flux.[16] Against all the background which would

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[15] *See, In re Mercier*, 515 F.2d 1161, 1166, 185 USPQ 774, 778 (CCPA 1975) where the court reversed a rejection of process claims in part stating:

> The relevant portions of a reference include not only those teachings which would suggest particular aspects of an invention to one having ordinary skill in the art, but also teachings which would lead such a person away from the claimed invention. (citation omitted)

[16] The Examiner has not formally relied on U.S. Patent No. 5,879,322 in any of the stated rejections. However, such patent does not teach the present invention by the description that a portion of the used device can be folded so that "**any** residual drug...can be safely sealed and, if desired, discarded." (emphasis added) Rather, the patent reinforces the present invention by recognizing that "any" residual amount is potentially hazardous which is what appellant has urged throughout the prosecution of the present application.

lead away from this discovery, appellant's invention is not suggested by the art and is clearly patentable thereover.

The Examiner's yet additional reliance on Muller et al is an extension of the "obvious to try" rationale. The patent has nothing to do with fentanyl administration which creates special concerns that are not present with other types of drugs. To take the position that one would load the reservoir with up to ten times the amount needed for administration would be invite the potential for misuse or abuse. Furthermore, one cannot ignore the teachings in the art which maintain that the rate of drug delivery is independent of concentration down to an extremely low level, well below that defined in the claims on appeal.[17] Thus, when combined with all the other documents discussed previously, Muller et al would not result in the method defined in the claims on appeal.

The Examiner has attempted to characterize the invention as a simple optimization situation. This is simply not true. Such a characterization ignores the fact that fentanyl presents special challenges and ignores the specific teachings in the art which would counsel away from the present invention by concluding that drug delivery is independent of concentration. As such, the current situation is similar to that which occurred in *In re Hedges*, 783 F. 2d 1038, 228 USPQ 685 (Fed. Cir. 1986) where the court considered claims relating to a process for sulfonating diphenyl sulfone in its molten state (about 127°C). One prior art reference (Felix) disclosed sulfonation at lower temperatures, but the PTO maintained that since the reference was an "open-ended" teaching with respect to temperature, determining the optimum temperature from this document alone was a matter

[17] On the other end of the spectrum, the 2% excess disclosed in Muller et al is probably too low to meet the concentration defined in the claims on appeal.

of "routine experimentation". The PTO nonetheless relied on further references which disclosed liquid phase reactions with temperatures being in the 160-180°C range in one instance and 115-140°C in another. The applicant contended that the Felix reference described a preference for lower temperatures and that adverse results were described at higher temperatures. The court reversed the rejection citing with approval decisions cautioning against picking and choosing from a reference. The court further stated:

> On balance, Hedges proceeded contrary to the accepted wisdom. This is "strong evidence of unobviousness".[18]

A further decision with implications on the present situation is *Key Pharmaceuticals Inc. v. Hercon Laboratories Corp.*, 161 F.3d 709, 48 USPQ2d 1911 (Fed. Cir. 1998). In that decision, the subject matter was a transdermal patch delivering nitroglycerin. A key recitation in the asserted claim was a sheet capable of retaining "sufficient pharmaceutically active drug to deliver to the skin a pharmaceutically effective amount ..over a 24-hour time interval". The phrase had been construed to mean delivering 2.5 to 15 milligrams of nitroglycerin per day.

The prior art relied on to invalidate the patent claims disclosed a patch delivering 2.0 milligrams of nitroglycerin per day. The court found unpersuasive the arguments that the prior art inherently anticipated or rendered obvious the asserted claim and upheld the validity of the claim.

Such decisions support the conclusion that in the present situation, the prior art cannot support a rejection of the claims on appeal.[19]

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[18] Citations omitted at 783 F.2d 1041, 228 USPQ 687.

[19] The foregoing case citations are also applicable to the other prior art rejections set forth below. The case law previously cited was simply for the legal principles annunciated therein (which are still correct) and not an attempt to analogize the facts with those in the

The Examiner has raised other arguments in an effort to justify the rejections. First, the Examiner has maintained that the present invention was derived from experimental worked necessary for FDA approval and "thus, on its face is obvious." Even if the Examiner's contention is correct, the genesis of the invention plays absolutely no role in the determination as to whether the invention is "obvious" under 35 U.S.C. §103. To contend, as the Examiner apparently has, that because an invention is developed as a part of a procedure to obtain governmental approval it is "on its face obvious" would be to directly ignore the statutory mandate in 35 U.S.C. §103(a) that:

> Patentability shall not be negatived by the manner in which the invention was made.

Therefore, this argument cannot be relied on to sustain any of the rejections of record.

The Examiner has also noted that the claims do not have an upper boundary for the drug concentration while contending that it would be obvious to load large amounts of drug into a reservoir to avoid continuous replacement. The Examiner is correct that the claims are not limited to any upper boundary of concentration. Based on the results illustrated in Figure 2, as long as the concentration is above about 16 mM, the desired results of the present invention can be obtained. Thus, there is no technical or legal requirement that an upper boundary be incorporated into the claims. As for the Examiner's contention that it would be obvious to add large amounts of drug into the donor reservoir, such assertion, even if true, would not necessarily lead to the present invention. As is evident from the discussion of the present invention set forth above, it is not a question of the concentration

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present appeal. Appellant respectfully maintains that the facts of the now cited decisions are closer than those surrounding the decisions discussed by the Examiner in the final Action.

of the drug at the start of the delivery period, but rather the concentration at the end of the total delivery period. Therefore, if one is designing a device that is to administer drug over a period of 30 days, it is logical that the amount of drug in the reservoir will be more than if the device is designed to deliver over a period of 10 days. However, in neither situation does it lead to an understanding that at the end the total drug delivery period, the concentration of fentanyl must be at the concentration defined in the claims on appeal.

D. Haak et al Does Not Inherently Anticipate The Presently Claimed Invention

The requirements of "inherency" are well settled. As stated in *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999):

> To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 126, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2d at 1749 (quoting *In re Oelrich,* 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

The Example of Haak et al relied on by the Examiner relates to a device which administers fentanyl by both passive (i.e., non-electrically assisted) diffusion at a rate of 25 μg/hr and iontophoretic delivery in an amount of 25 μg every 5 minutes. Column 14, line 51 then concludes: "Thus, when the electrically assisted portions are activated, the total fentanyl delivery rate from the system is about 325 μg/hr." The Examiner's rationale is that since the device must act in a linear fashion to make this statement, it must inherently meet the claims.

The Examiner's position ignores the fact that Haak et al does not state that the device is to be operated for a total of only one hour.[20] The patent example does not provide the total period of operation and is silent about the delivery rate at any later time frame, be it the second, twenty fourth, or one hundredth hour. In view of the disclosed presence of three lithium batteries in the Example (column 14, lines 14-15), there is nothing to dispute the possibility that the device can operate for a substantial period of time, such as until the reservoir is depleted. Thus, in view of the requirement of inherency that the result can not be established by probabilities or possibilities, it is without question that Haak et al does not inherently meet any of the claims on appeal.

E. The Combination of Haak et al, Rebinder, The '894 Patent, Muller et al and Newman Also Would Not Result in the Presently Claimed Invention

The Examiner has relied on Rebinder, the '894 patent and Muller et al for the same reasons as in the first combination and appellant believes that the reasons as to why these documents do not establish a *prima facie* case of obviousness has likewise been addressed above. Considering the art as a whole with the recognition of the potential dangers of fentanyl and the stated understanding in the art that the delivery rate is independent of concentration, those of ordinary skill in the art would not arrive at appellant's claimed invention from the combined disclosures of the first four cited documents.

The Examiner's further reliance on Newman marks an attempt to misinterpret the teachings set forth in the art in an effort to meet the recitations set forth in the claims on appeal. The Examiner has specifically referred to the passage starting at column 7, line 46 which indicates that the application of pain killing drugs in the disclosed iontophoresis drug

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[20] 25 μg/hr + (12 x 25 μg/5 min) = 325 μg/hr

delivery system can be monitored and controlled by monitoring the patient's heartbeat and that a microprocessor can be used to permit the patient to self-administer medication and to require intervening non-administration periods between doses of the drugs.

Even if one were to combine the teachings of Newman with those of Haak et al and the other cited references, one would still not arrive at the presently claimed invention. The teachings of Newman would lead to a device wherein the rate of administration of the drug is controlled. There is nothing in the patent which would lead to a method wherein the total drug delivery permitted by the system is terminated while a substantial amount of the drug, particularly a potent drug such a fentanyl, remains in the donor reservoir. Indeed, the Examiner's statement that the patent could provide for treatment for days on end could just as well result in a total depletion of the donor reservoir. There is nothing in Newman which would lead to the defined concentration or an understanding as to why this concentration is important in the context of the present invention. Thus, the still further reliance on Newman would not lead to the invention defined by the claims on appeal.

F. The Claims of Theeuwes et al Do Not Anticipate The Claimed Invention

The method claims of Theeuwes et al relate to a method of inducing analgesia using fentanyl, sufentanil or analogues of either using an electrotransport device. There is no recitation of concentration throughout the total delivery period as required in the claims nor is there any recitation of delivery rate or duration. Yet, the Examiner has considered the claims on appeal to be inherent from the claims of the patent. The requirements of inherency have been discussed above and, given the total absence of any specificity in the claims of the patent, it is evident that inevitability that "inherency" demands is not present.

If the Examiner is taking the position that the broad nature of the claims of Theeuwes et al is alone sufficient, then this argument is legally flawed in view of the holding in *In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985) where the court held that an assertion that a prior art patent claim is broad enough to read on a claimed invention does not require conclusion of obviousness since the scope of the claim determines what infringes and is no measure of what it discloses. If it is insufficient for obviousness, then it goes without saying that it is insufficient for anticipation.

The Examiner has also referred to the specification of Theeuwes et al and has specifically stated:

> Although the specification of Theeuwes provides little information for such a method and device, the examiner still considers it inherent.

The admission that Theeuwes et al does not provide sufficient specificity concerning the subject matter defined in the claims on appeal is believed to alone be sufficient to defeat a position of inherency. The patent does not teach the defined concentration must be maintained throughout the entire delivery period and quite clearly does not recognize the importance of this concentration that has been illustrated in Figure 2 of the present application. Therefore, Theeuwes et al cannot be relied on to anticipate the claims on appeal.

G. The Combination of Theeuwes et al, Rebinder, The '894 Patent, Muller et al and Newman Would Not Result in the Presently Claimed Invention

The admission that Theeuwes et al does not provide sufficient specificity concerning the subject matter defined in the claims on appeal also has a bearing on the propriety of the "obviousness" rejection under 35 U.S.C. §103. It will be recalled from the discussion provided above that the Examiner has noted with respect to the '739 patent that such patent,

"like others fail to specify the particulars of the drug concentration as defined in the claimed invention." This is certainly true with respect to Theeuwes et al which primarily is concerned with the membrane used in the disclosed delivery device. While appellant agrees with the Examiner that Theeuwes et al does not provide sufficient specificity with respect to the claimed invention, the patent does suggest in the passage beginning at column 7, line 43 that it may be advantageous to operate at a low donor drug concentration depending on certain characteristics of the membrane. Accordingly, such passage would tend to counsel away from invention, particularly in light of the known characteristics of fentanyl.

The respective teachings of Rebinder, the '894 patent, Muller et al and Newman have all been discussed above and there is no need to discuss them all again. Suffice it to state here that at best such documents create an "obvious to try" situation which is fatal to a rejection based on 35 U.S.C. §103. When the deficiencies of these documents are considered together with the documents that maintain that drug delivery rate is independent of concentration, it is without question that this final hypothetical combination of documents also is insufficient to justify a rejection of any of the claims on appeal.

H. The Claims On Appeal Are Patentable Over the Claims of Southam et al

Southam et al does not constitute "prior art" against the present application. For "obviousness-type" double patenting purposes, the test is not whether the claims in one case are broader than in another, but whether the claimed invention in the subject application would have been obvious from the subject matter of the claims in the other case in light of

the prior art.[21] In making this determination, it is important to keep in mind that one cannot use the specification of the prior patent as "prior art".[22]

Southam et al claims a method of obtaining self-administered analgesia by defining the dosage of fentanyl, the delivery period and the total number of additional doses over a period of 24 hours. The claims of Southam et al do not lead to any understanding that when the final additional dose is applied, the concentration of fentanyl salt remaining in the donor reservoir must be above about 16 mM. In fact, it is entirely within the scope of the claims of Southam et al that the final fentanyl dose can be from a donor reservoir which contains a fentanyl salt concentration well below 16 mM. Indeed, there is absolutely nothing in the claims of Southam et al which indicates any residual level of fentanyl in the donor reservoir.

The Examiner has referred to claim 6 which recites that the amount of fentanyl salt comprises 1.9 to 2.0 wt % of the formulation. This claim does not specify how much formulation is present and it is certainly possible that the amount of formulation could be present so that the when the final dose is administered, the concentration of fentanyl is below the level recited in the claims on appeal. To take the position that the amount of formulation should be selected such that when the amount of fentanyl salt is 1.9 to 2.0 wt % and when the quantity per dose and total number of doses are selected so that the remaining fentanyl concentration meets that defined in the claims on appeal would be to again rely on an "obvious to try" standard which is just as fatal to a determination of "obviousness" in a double patenting situation as it is in the context of 35 U.S.C. §103.

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[21] *Ex parte Oetiker*, 23 USPQ2d 1651 (Bd. Pat. App. Inter. 1990), *affirmed*, 23 USPQ2d 1661 (Fed. Cir. 1991) (unpub).

[22] *In re Kaplan*, 789 F.2d 1574, 229 USPQ 678 (Fed. Cir. 1986).

Thus, one would simply not arrive at the presently claimed invention defined by claims 1, 4 and 7-9 from the claims of Southam et al and it follows that these claims of the present application are patentable over the patent claims.

I. Claim 9 Is Further Patentable Over the Prior Art

Independent claim 1 requires that the defined fentanyl concentration above about 16 mM is maintained "substantially throughout the total analgesic drug iontophoretic delivery period wherein the analgesic drug is delivered through the body surface." Dependent method claim 9 further specifies that the electrotransport flux is substantially proportional to a level of electrotransport current applied by the delivery device during the iontophoretic drug delivery.

As discussed above, the cited prior art does not disclose that fentanyl delivery from an iontophoretic delivery device should be terminated upon completion of the total delivery period while a substantial amount of fentanyl remains in the donor reservoir. The prior art teaches that drug delivery is independent of drug concentration down to a very low level. Given the characteristics of fentanyl, the art would tend to suggest that one should avoid high residual concentrations to avoid possible concerns with the used device. In contrast and as illustrated in Figure 2, once the concentration of fentanyl falls below the defined level, which is the result of fentanyl being depleted from the reservoir, the iontophoretic flux significantly decreases and is no longer substantially proportional to the level of iontophoretic current applied during drug delivery. Accordingly, this aspect of the invention is also not disclosed or suggested by the cited prior art and marks a further distinction thereover which must be separately considered.

X. CONCLUSION

For the reasons set forth above, appellant respectfully submits that when the claims are properly interpreted and the actual teachings of the prior art compared, including teachings that caution about the dangers of residual fentanyl in used devices, it is clear that appellant has made a significant discovery that enables effective fentanyl delivery by iontophoresis. Accordingly, appellant respectfully submits that the presently claimed invention is not anticipated by the documents, especially if reliance is placed on the principle of inherency, and is not rendered obvious by the various combinations of art set forth in the final Action or by the claims of Southam et al. In addition, appellant maintains that claim 9 is further patentable over the prior art. Accordingly, appellant respectfully requests reversal of each of the rejections on appeal.

Respectfully submitted,

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APPENDIX A

CLAIMS ON APPEAL

1. In a method of delivering an analgesic drug selected from the group consisting of fentanyl salts through a body surface by iontophoresis from a delivery device having a donor reservoir containing an at least partially aqueous solution of a fentanyl salt, the improvement comprising maintaining the concentration of the salt in solution above a level at which the iontophoretic flux of the drug is dependent on the concentration of the drug salt in the solution, said level of said fentanyl salt being above about 16 mM, the concentration of the salt in the solution being maintained substantially throughout the total analgesic drug iontophoretic delivery period wherein the analgesic drug is delivered through the body surface.

4. The method of claim 1, wherein the donor reservoir comprises a hydrogel containing an aqueous fentanyl salt solution, the solution having a fentanyl concentration above 6 mg/mL in the hydrogel.

7. The method of claim 1, wherein the body surface is intact skin.

8. The method of claim 1, wherein the body surface is intact human skin.

9. The method of claim 1, wherein the iontophoretic flux of the analgesic drug is substantially proportional to a level of current applied by the delivery device during the iontophoretic drug delivery.

APPENDIX B

COMMENTARY

TF-210

Disposal of used fentanyl patches

ASH B. YERASI, JOHN D. BUTTS, AND JOHN D. BUTTS

Am J Health-Syst Pharm. 1997; 54:85-6

Fentanyl is a potent opioid that has been abused both on the street and by health care professionals.[1-3] The transdermal delivery system for fentanyl (the fentanyl patch) can be abused even after it has been discarded. We describe here a case of transdermal fentanyl abuse and discuss how existing laws and practices fail to make used patches inaccessible. We also offer recommendations for the proper disposal of transdermal fentanyl.

Case report

A 31-year-old man collapsed face down on the bank of a pond while fishing. He had complained of weakness and nausea before collapsing, and his companion's attempts to rouse him were unsuccessful. Emergency personnel arrived 10 minutes later and found the man to be diaphoretic, cyanotic, and breathing shallowly twice a minute. The blood pressure was 210/110 mg Hg, and the heart rate was extremely high (rate unrecorded). Bowel sounds and the gag reflex were absent. The patient was intubated and brought to the hospital emergency department in cardiac arrest. Resuscitative efforts, which included the administration of sodium bicarbonate, epinephrine, lidocaine, and intravenous fluids, were unsuccessful, and the patient was pronounced dead 103 minutes after his collapse.

The patient had been taking propoxyphene with acetaminophen for migraine headaches. A few weeks before his death he had undergone a root canal procedure and received unspecified analgesics (but not fentanyl). He had worked as a transporter for a funeral home.

Postmortem toxicological studies were negative for the presence of ethanol, cocaine, morphine, volatile agents, and organic bases; trace amounts of propoxyphene and its metabolite norpropoxyphene were detected. The serum fentanyl concentration was 15 µg/L. (Normal therapeutic concentrations of fentanyl range from 1 to 3 µg/L, and central nervous system depression occurs in this range.[2] The fentanyl concentration in suicidal and accidental overdoses is often less than 5 µg/L.) The serum lidocaine concentration was 2 mg/L, consistent with the administration of the drug during the attempted resuscitation. Death was attributed to fentanyl poisoning.

The medical examiner's investigation revealed that the most likely source of the decedent's fentanyl was two used transdermal fentanyl patches (one 75-µg/hr and one 100-µg/hr patch [Duragesic, Janssen]). The decedent had on the day of his death transported the body of a recently deceased woman from a local nursing home. The patches had been applied the previous day but not been removed before the body was transported. The nursing home had no policy concerning removal of patches from deceased patients. If the patches had been worn by the woman for 24 hours, then the patches would theoretically have had about 13.3 mg of fentanyl remaining in them.

Disposal of fentanyl patches

Published reports make it clear that transdermal fentanyl can be abused,[4,5] yet the laws regarding its disposal are vague. Federal law does not describe the actual manner in which controlled substances in general should be destroyed, and there are no specific regulations on how used fentanyl patches should be destroyed or made unavailable to unauthorized persons (Black JR, Drug Enforcement Administration, personal communication, 1996 Apr 18). Individual states are generally no more specific in describing the proper destruction of controlled substances.

We reviewed the procedures for the disposal of used fentanyl patches at two academic teaching hospitals in North Carolina. In some instances used patches were cut before being discarded in the trash, and in others they were flushed down the toilet. Most commonly,

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The assistance of Maryann D. Oertel, Pharm.D., BCPS, and Priya B. Yerasi, M.D., is acknowledged.

the patches were simply discarded unaltered (not necessarily into the biohazard waste receptacle).

The lack of adequate federal and state regulatory controls and the resultant laxity in disposal make used fentanyl patches relatively easy to obtain at health care facilities. Institutional initiatives for the appropriate disposal of the patches, if they necessitate substantial documentation, may not be readily accepted by health care professionals already overburdened with paperwork. Nevertheless, adequate disposal of used patches might prevent some illicit use and reduce the expenditures associated with fentanyl abuse.

Recommendations

Education would be a reasonable first step in addressing the problem of fentanyl patch abuse. Health care providers could be taught about the potentially lethal amounts of fentanyl remaining in used patches and about the patches' unique pharmacokinetic properties.

The key to proper patch disposal is the institution of procedures that make discarded patches unusable and that comply with applicable laws (as those laws concern, for example, the persons authorized to destroy controlled substances and the need for witnesses and cosignatures). The most foolproof method would be to collect from all patients all used narcotics, which would then be incinerated. In institutions without an incinerator, used patches collected from inpatients could either be cut and flushed down the toilet or placed in separately marked biohazard waste receptacles. Cutting the patch before flushing would allow the gel to diffuse in sewage water such that the amount of drug left in a found patch fragment would be reduced. If patches are cut, gloves should be worn to prevent the gel from touching the skin of the health care worker and being absorbed, and the scissors should be cleaned with alcohol afterward. Another possibility would be an exchange program in which used or unused patches were turned in before new patches or other controlled substances were dispensed.[5,6]

Outpatients should be strongly encouraged to follow the manufacturer's directions for patch disposal. The manufacturer states that unneeded patches should be flushed down the toilet—used ones after being folded so that the adhesive side sticks to itself, and unused ones after being removed from the pouch.[7] Cutting patches into several pieces before flushing may be reasonable for outpatients who want to ensure that no one in the immediate vicinity has access to a discarded patch. Again, gloves should be worn, and the scissors should be cleaned after the cutting.

Conclusion

Fentanyl patches, if not disposed of properly, can be abused and cause harm or death. Federal and state laws and most institutional procedures do not ensure that used patches are rendered unusable. Health care professionals should institute practices that make the abuse of discarded fentanyl patches impossible.

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CASE REPORT

Leslie E. Edinboro,[1] M.S.; Alphonse Poklis,[1] Ph.D.; Donna Trautman,[2] B.S.; Sybil Lowry,[2] B.S.; Ronald Backer,[2] Ph.D.; and Charles M. Harvey,[3] M.D.

Fatal Fentanyl Intoxication Following Excessive Transdermal Application*

REFERENCE: Edinboro LE, Poklis A, Trautman D, Lowry S, Backer R, Harvey CM. Fatal fentanyl intoxication following excessive transdermal application. J Forensic Sci 1997;42(4):741–743.

ABSTRACT: The case history and toxicological findings of a fatal fentanyl intoxication due to the application of multiple transdermal patches are presented. An 83 year-old white female with terminal cancer was found dead with three 100 mg/h fentanyl patches on her chest. The autopsy and subsequent histological studies revealed extensive areas of gastric carcinoma, a large atrial tumor, ulceration of esophagus, metastasis of peripancreatic lymph nodes and a recent surgical removal of part of the lower lobe of the left lung. Toxicological analysis by GC/MS yielded fentanyl concentrations of blood, 25 ng/mL; brain, 54 ng/g; heart 94 ng/g; kidney 69 ng/g; and liver 104 ng/g. The cause of death was determined to be fentanyl overdose and the manner of death was ruled undetermined as the investigation was unable to conclusively establish whether this was an accidental overdose, a suicide, an assisted suicide, or possibly a homicide. This case demonstrates the need for caution in self-administration of transdermal fentanyl patches, in particular, the dangers inherent in the application of multiple patches which can result in the release of potentially toxic or lethal doses.

KEYWORDS: forensic science, forensic toxicology, death, fentanyl, transdermal administration, drug overdose, poisoning

Fentanyl is a synthetic narcotic analgesic of high potency (80 times morphine) and short duration of action (1). Due to lessened side effects, including shorter duration of respiratory depression, fentanyl is the analgesic of choice in surgical procedures performed in the U.S.A. Plasma concentrations of fentanyl of 2 to 5 ng/mL are sufficient to induce surgical analgesia and respiratory depression (2). In addition to use as a surgical analgesic, fentanyl is also prescribed for the management of chronic pain for patients requiring opiate analgesia. Recently, fentanyl has become available in 2.5, 5, 7.5, and 10 mg transdermal patches which release 25, 50, 75, and 100 μg/hr, respectively, for over 72 h (3). Measurable serum concentrations of fentanyl occur within 2 h of application of the patches (4). Blood, serum, and plasma concentrations are similar to those obtained following equivalent I.V. doses (3,5). Fentanyl has a large apparent volume of distribution (60–300 L) and is primarily metabolized in the liver by dealkylation (2). The elimination of fentanyl is highly dependent on the age and physiological status of the patient.

Fentanyl's therapeutic popularity has not been without problems. As a potent narcotic, fentanyl has become an abuse problem among health professionals, including anesthesiologists, physicians, pharmacists, and nurses (6,7). Recreational abuse of fentanyl is extremely dangerous due to the low concentrations necessary to induce respiratory depression. Several overdose deaths of health professionals have been reported (8–11).

More recently, however, recreational abuse of fentanyl by non-health professionals has been reported involving ingestion, injection, or smoking of fentanyl transdermal patches (12–14). As the use of transdermal patches increases for the management of chronic pain, it appears that other forms of therapeutic mis-adventures may be occurring. For example, patients may apply more than one patch at a time in order to experience enhanced pain relief. As the patches are capable of delivery therapeutic doses of fentanyl, placement of multiple patches would result in fentanyl toxicity including death.

The following case is presented as an example of fentanyl toxicity, as a direct result or compounding factor, in the death of an elderly woman found with multiple fentanyl transdermal patches on her body.

Case Report

Autopsy Findings

An 83-year-old white female was found dead with three 100 ug/h fentanyl patches on her chest. The woman had been diagnosed with terminal cancer and was using fentanyl patches for treatment of pain. The autopsy and subsequent histological studies revealed extensive areas of gastric carcinoma, a large antral tumor, ulceration of esophagus, metastasis of peripancreatic lymph nodes and a recent surgical removal of part of the lower lobe of the left lung. A careful examination of the body revealed no apparent injection sites.

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Toxicological Analysis

Initial Analysis—Blood was initially screened for ethanol using an enzymatic/radiant energy technique; salicylates by trinders reagent and morphine by radioimmunoassay (RIA). Urine as analyzed for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and phencyclidine by enzyme immunoassay (Emit II, Bahring Diagnostics, San Jose, CA). Additionally, both blood and urine were screened for fentanyl by RIA (Diagnostic Products, Los Angles, CA) (15).

Quantitative Fentanyl Analysis

GC/MS quantitation of fentanyl was based on previously published methods (16–18). To separate 5.0 g samples of heart, liver, kidney, and brain tissue were added 5.0 mL of distilled water. The samples were then homogenized in a mini-adapted Waring Blender. To 5.0 mL aliquots of tissue homogenates and 2.0 mL aliquots of calibrators, drug free blood, and autopsy blood samples was added 50 ng/mL of fentanyl-d5 (Radian Corp. Austin, TX) as the internal standard. To each aliquot 2.0 mL of pH 9 saturated borate buffer was added, followed by 8.0 mL of n-chlorobutane. The aliquots were vortexed for 15 min, then centrifuged for 5 min and the organic top layer was drawn off into a new tube. Then 2.0 mL 0.1M HCl was added to each extract which was the vortexed for 15 min and centrifuged for 5 min. The bottom aqueous layers were then removed using a 2 mL glass pipette and placed into clean 15 mL centrifuge tubes. The pH of the solutions were then adjusted to greater than pH 9 with the addition of 1.0 mL of 2 N NaOH. The solution was extracted with 3.0 mL of n-chlorobutane by vortexing for 10 min followed by centrifuging for 5 min and organic layers were then transferred to clean 12 by 75 mm test tubes and evaporated to dryness in a Savant Evaporator/Concentrator for 20 min (initial 10 min with radiant cover on). The residues were reconstituted with 500 μL n-chlorobutane, vortexed, and evaporated to dryness at 80°C under dry nitrogen. The resultant residues were reconstituted with 50 μL of n-chlorobutane of which 2.5 μL aliquots were injected into the GC/MS.

GC/MS analysis was performed on a Hewlett-Packard (Avondale, CA) 5890 GC equipped with a 12.5 m by 0.2 mm (ID) by 0.33 μm (film thickness) cross linked 5% phenyl silicone capillary column with a 12 m guard column (Restek, Bellefonte, PA) connected to a Hewlett-Packard 5971-A mass selective detector. Data processing was performed with a HP Chemstation (Version 3.2 software) in the scan mode monitoring m/z ions from 44–600. The GC/MS was operated in the splitless mode with a helium carrier gas linear velocity of 20 mL/min. Initial oven temperature was 200°C for 1 min with an injection port temperature of 250°C. The temperature was ramped at 15°C/min to a final temperature of 280°C which was held for 2.5 min. Data were collected in the SIM mode monitoring m/z ions 245, 146, 189 (fentanyl) and 250, 151, 194 (fentanyl-d5) with a dwell time of 50 ms for each ion.

Calibration

Fentanyl working standard (1 μg/mL) was prepared by diluting 1:100 with methanol a 100 μg/mL fentanyl stock standard (Radian Corp.). A calibration curve (0.5, 2.0, 10.0, and 50.0 ng/mL fentanyl) was prepared by adding the appropriate volume of fentanyl working standard to 2.0 mL of drug free whole blood. The calibrators were vortexed and allowed to equilibrate 1 h prior to use.

Results

Initial toxicological analysis of blood and urine failed to disclose the presence of commonly encountered drugs of abuse and alcohol. RIA fentanyl analysis yielded 14 ng/mL in urine and 10 ng/mL in blood (extrapolated from the urine calibration curve). The results of GC/MS fentanyl analysis of the decedents' blood and tissues are presented in Table 1. Fentanyl blood and tissue concentrations greatly exceed those associated with therapeutic administration (4–6) and are consistent with or greatly exceed those previously reported in cases of fatal intoxication (8–11,14,19,20). Fentanyl blood concentrations in these cases ranged from 0.1–28 ng/mL with liver and kidney valves ranging up to 76 and 42 ng/mL, respectively.

The cause of death was determined to be fentanyl overdose and the manner of death was ruled undetermined. The investigation was unable to conclusively establish whether this was an accidental overdose, a suicide, an assisted suicide, or possibly a homicide.

Discussion

The use of fentanyl transdermal release patches provides the advantages of maintaining a constant therapeutic serum concentration similar to constant I.V. infusion while circumventing erratic gastrointestinal absorption and first pass metabolism of oral preparations (3,4). Thus, these dosage forms have proven efficacious for the long term management of cancer related pain. No doubt the out-patient prescribing of transdermal patches will increase in the future. To prevent fentanyl toxicity, both patient and care giver must be properly instructed on the use and hazards of fentanyl patches.

In this case, the decedent was instructed to apply one 100 ug/h patch once every 2–3 days as indicated for cancer related pain. Application of a single 100 μg/h transdermal fentanyl patch would be expected to result in a maximal plasma fentanyl concentrations of 2 to 3.8 ng/mL at 25–72 h after application (4). It appears that the application of multiple transdermal fentanyl patches resulted in an overdose for this woman. Theoretically, three 100 μg/h patches would be expected to produce a blood fentanyl concentration of approximately 10 ng/mL within 24 h of application. The blood concentration of fentanyl in this case was 25 ng/mL indicating that this woman may have been using multiple patches for several days. Additionally, due to her age, the metabolism of fentanyl may have been markedly decreased. Therefore it is possible that the time frame for development of toxicity would have been shortened. The high concentrations of fentanyl in the tissues may also indicate reduced metabolism. Unfortunately, we did not analyze the specimens for fentanyl metabolites as primary reference materials were unavailable from commercial supplies and request to the manufacturer of the drug were not answered. Clearance of unchanged fentanyl via the kidney is less than 8% of an I.V. dose. In this case, kidney concentrations were higher than

TABLE 1—*Toxicological findings.*

Tissue	Fentanyl Concentration
Blood	25 ng/mL
Brain	54 ng/g
Heart	94 ng/g
Kidney	69 ng/g
Liver	104 ng/g

previously reported cases involving I.V. deaths. This high concentration would not be expected under normal conditions for a transdermal delivery system and could be the result of increased unchanged fentanyl available for excretion via the kidneys.

Conclusion

This case demonstrates the need for caution in self-administration of transdermal fentanyl patches, in particular, the dangers inherent in the application of multiple patches which can result in the release of potentially toxic or lethal doses. This same caution would apply to nonprofessional care givers assisting in the application of fentanyl patches. It is important to keep in mind that the metabolism of fentanyl in the elderly is slowed and must be considered as a factor in the high concentrations achieved in this case. The potential for misuse of transdermal fentanyl patches (foul play, assisted suicide, and therapeutic mis-adventures) must be considered in any death associated with fentanyl toxicity.

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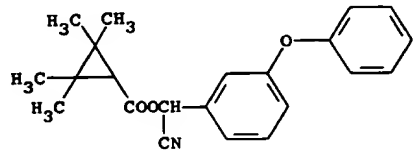
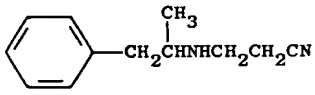
3921. Fenpropathrin. *2,2,3,3-Tetramethylcyclopropane carboxylic acid cyano(3-phenoxyphenyl)methyl ester;* α-cyano-3-phenoxybenzyl 2,2,3,3-tetramethylcyclopropanecarboxylate; fenpropanate; meothrin; S 3206; SD 41706; WL 41706; Danitol. $C_{22}H_{23}NO_3$; mol wt 349.43. C 75.62%, H 6.63%, N 4.01%, O 13.74%. Synthetic pyrethroid insecticide with repellant and contact activity. Prepn: T. Matsuo *et al.*, Ger. pat. **2,231,312** corresp to U.S. pat. **3,835,176** (1973, 1974 to Sumitomo). Metabolism: M. J. Crawford, D. H. Hutson, *Pestic. Sci.* **8**, 579 (1977). Degradn in soil: T. R. Roberts, M. E. Standen, *ibid.* 600.



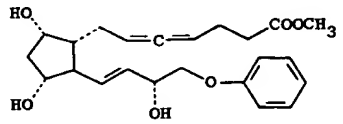
Pale yellow oil, n_D^{26} 1.5283.
USE: Insecticide, acaricide.

3922. Fenproporex. *3-[(1-Methyl-2-phenylethyl)amino]propanenitrile; 3-[(α-methylphenethyl)amino]propionitrile;* (±)-*N*-2-cyanoethylamphetamine. $C_{12}H_{16}N_2$; mol wt 188.27. C 76.55%, H 8.57%, N 14.88%. Deriv of amphetamine, *q.v.* Prepn: Fr. pat. **M4364** corresp to P. Pohrbach, J. Blum, U.S. pat. **3,485,924** (1966, 1969 both to Bottu). Pharmacological studies: B. M. Beecham *et al.*, *J. Pharm. Pharmacol.* **23**, 140 (1971); A. H. Beckett *et al.*, *ibid.* **24**, 194 (1972). Peripheral effects in human and rat adipose tissue: M. Dubost *et al.*, *Brit. J. Pharmacol.* **58**, 436P (1976). Chromatographic identification of amphetamine in urine of patients treated with fenproporex: R. B. Sznelvar, *Eur. J. Toxicol. Environ. Hyg.* **8**, 5 (1975). Clinical trial: G. Hertel, W. Fallot-Burghardt, *Fortschr. Med.* **96**, 2380 (1978).



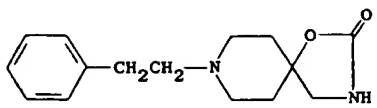
Liquid, bp_2 126-127°.
Hydrochloride, $C_{12}H_{17}ClN_2$, ***Gacilin, Solvolip.*** White, cryst, odorless powder from abs ethanol, mp 146°. Bitter taste. Sol in water, 95% ethanol.
Diphenyl acetate, $C_{26}H_{28}N_2O_2$, ***Fenproporex Retard Bottu.***
THERAP CAT: Anorexic.

3923. Fenprostalene. *7-[3,5-Dihydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)cyclopentyl]-4,5-heptadienoic acid methyl ester;* (±)-9α,11α,15α-trihydroxy-16-phenoxy-17,-18,19,20-tetranorprosta-4,5,13-*trans*-trienoic acid methyl ester; RS-84043; Bovilene; Synchrocept B. $C_{23}H_{30}O_6$; mol wt 402.49. C 68.64%, H 7.51%, O 23.85%. Synthetic analog of prostaglandin $F_{2\alpha}$, related structurally to prostalene, *q.v.* Prepn: J. M. Muchowski, J. H. Fried, U.S. pat. **3,985,791**; A. R. Van Horn *et al.*, U.S. pat. **4,178,457** (1976, 1979 both to Syntex). Effect on pregnancy in beagles: B. Vickery, G. Mc Rae, *Biol. Reprod.* **22**, 438 (1980). Duration of action study: B. H. Vickery *et al.*, *Prostaglandins Med.* **5**, 93 (1980).



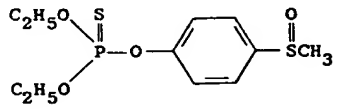
uv max (methanol): 220, 265, 271, 278 nm (log ε 3.99, 3.11, 3.23, 3.16).
THERAP CAT (VET): Luteolysin.

3924. Fenspiride. *8-(2-Phenylethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one;* decaspiride; DESP. $C_{15}H_{20}N_2O_2$; mol wt 260.33. C 69.20%, H 7.74%, N 10.76%, O 12.29%. Prepn: Neth. pat. **Appl. 6,504,602** corresp. to Regnier *et al.*, U.S. pat. **3,399,192** (1965 and 1968, both to Sci. Union et Cie-Soc. Franc. Recherche Méd.). Pharmacology: LeDouarec *et al.*, *Arzneimittel-Forsch.* **19**, 1263 (1969); Duhault *et al.*, *ibid.* **22**, 1947 (1972).



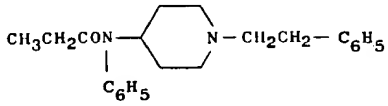
Hydrochloride, $C_{15}H_{21}ClN_2O_2$, ***NAT-333, NDR-5998A, Espiran, Pneumorel, Respiride, Tegencia, Viarespan.*** Crystals decomp 232-233°. Soluble in water. LD_{50} i.v. in mice: 106 mg/kg; orally in rats: 437 mg/kg.
THERAP CAT: Bronchodilator, antiadrenergic (α-receptor).

3925. Fensulfothion. *Phosphorothioic acid O,O-diethyl O-[4-(methylsulfinyl)phenyl] ester;* O,O-diethyl O-[*p*-(methylsulfinyl)phenyl] phosphorothioate; BAY 25/141; Dasanit; Terracur P. $C_{11}H_{17}O_4PS_2$; mol wt 308.35. C 42.85%, H 5.56%, O 20.75%, P 10.04%, S 20.79%. Prepn: Homeyer, Schrader, **Belg. pat. 666,012** (1965 to Bayer), *C.A.* **64**, 20555f (1966).



Liquid. $b_{0.01}$ 138-141°. LD_{50} orally in rats: 5 mg/kg.
Note: For application 1 part of fensulfothion may be mixed with 0.5 part xylene, 0.6 part emulsifier added and the mixture diluted with water. An effective concn of 10 to 40 ppm is claimed.
USE: Nematocide, insecticide; esp for the control of nematodes in golf courses and cemeteries. A 10% granular formulation is available for the control of onion maggots.

3926. Fentanyl. *N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide; N-(1-phenethyl-4-piperidyl)propionanilide;* N-(1-phenethyl-4-piperidinyl)-*N*-phenylpropionamide; R 4263; Leptanal. $C_{22}H_{28}N_2O$; mol wt 336.46. C 78.53%, H 8.39%, N 8.33%, O 4.76%. Prepn: Janssen, Gardocki, U.S. pat. **3,141,823** (1964 to Janssen). Pharmacology: Gardocki, Yelnosky, *Toxicol. Appl. Pharmacol.* **6**, 48 (1964); Hess *et al.*, *J. Pharmacol. Exp. Ther.* **179**, 474 (1971). Effects on cerebral circulation and metabolism in rats: C. Carlsson *et al.*, *Anesthesiology* **57**, 375 (1982). Clinical studies: E. A. Welchew, J. A. Thornton, *Anaesthesia* **37**, 309 (1982); M. J. Stephens *et al.*, *Med. J. Aust.* **1**, 419 (1982).



Crystals, mp 83-84°.
Citrate, $C_{28}H_{36}N_2O_8$, ***phentanyl, Fentanest, Pentanyl, Sublimaze.*** Crystalline powder, mp 149-151°. Bitter taste. One gram dissolves in about 40 ml water. Sol in methanol; sparingly sol in chloroform. LD_{50} in mice: 11.2 mg/kg i.v.; 62 mg/kg s.c., Gardocki, Yelnosky, *loc. cit.*
Note: A potent deriv, 3-methylfentanyl, has been erroneously referred to as "China White", a street term for very pure Southeast Asia heroin, *see Chem. & Eng. News* **59**, 71 (Jan. 19, 1981).
Caution: Abuse leads to habituation or addiction.
THERAP CAT: Analgesic (narcotic).
THERAP CAT (VET): The citrate as analgesic, tranquilizer.

3927. Fenthion. *Phosphorothioic acid O,O-dimethyl O-[3-methyl-4-(methylthio)phenyl] ester;* O,O-dimethyl O-(4-methylmercapto-3-methylphenyl) thionophosphate; O,O-dimethyl O-(3-methyl-4-methylthiophenyl) thiophosphate; O,O-dimethyl O-(4-methylthio-3-methylphenyl) thiophosphate; O,O-dimethyl O-[4-(methylthio)-*m*-tolyl] phosphorothioate; 4-methylmercapto-3-methylphenyl dimethyl thiophosphate; Bayer 29493; ENT 25540; S 1752; Baycid; Baytex; Entex; Lebaycid; Mercaptophos; Queletox; Spotton; Talodex; Tiguvon. $C_{10}H_{15}O_3PS_2$; mol wt 278.34. C 43.15%, H 5.43%, O 17.25%, P 11.13%, S 23.04%. Prepn:

Russia Confirms Suspicions About Gas Used in Raid

Potent Anesthetic Pumped Into Theater

2 More Hostages Die From Drug's Effects

Article 8 of 9 found

Susan B. Glasser and Peter BakerWashington Post Foreign Service
October 31, 2002; Page A15
Section: A
Word Count: 905

The Russian Health Ministry today belatedly identified the gas that killed more than 100 hostages at a Moscow theater during a rescue attempt last weekend as a powerful form of the opioid drug fentanyl. The official acknowledgment, days after Western experts said they suspected fentanyl was the substance used. came as the hostage death toll from the effects of the gas rose by two, to 117. Moscow health officials said two other hostages were killed by gunfire during the 58hour standoff

APPENDIX C

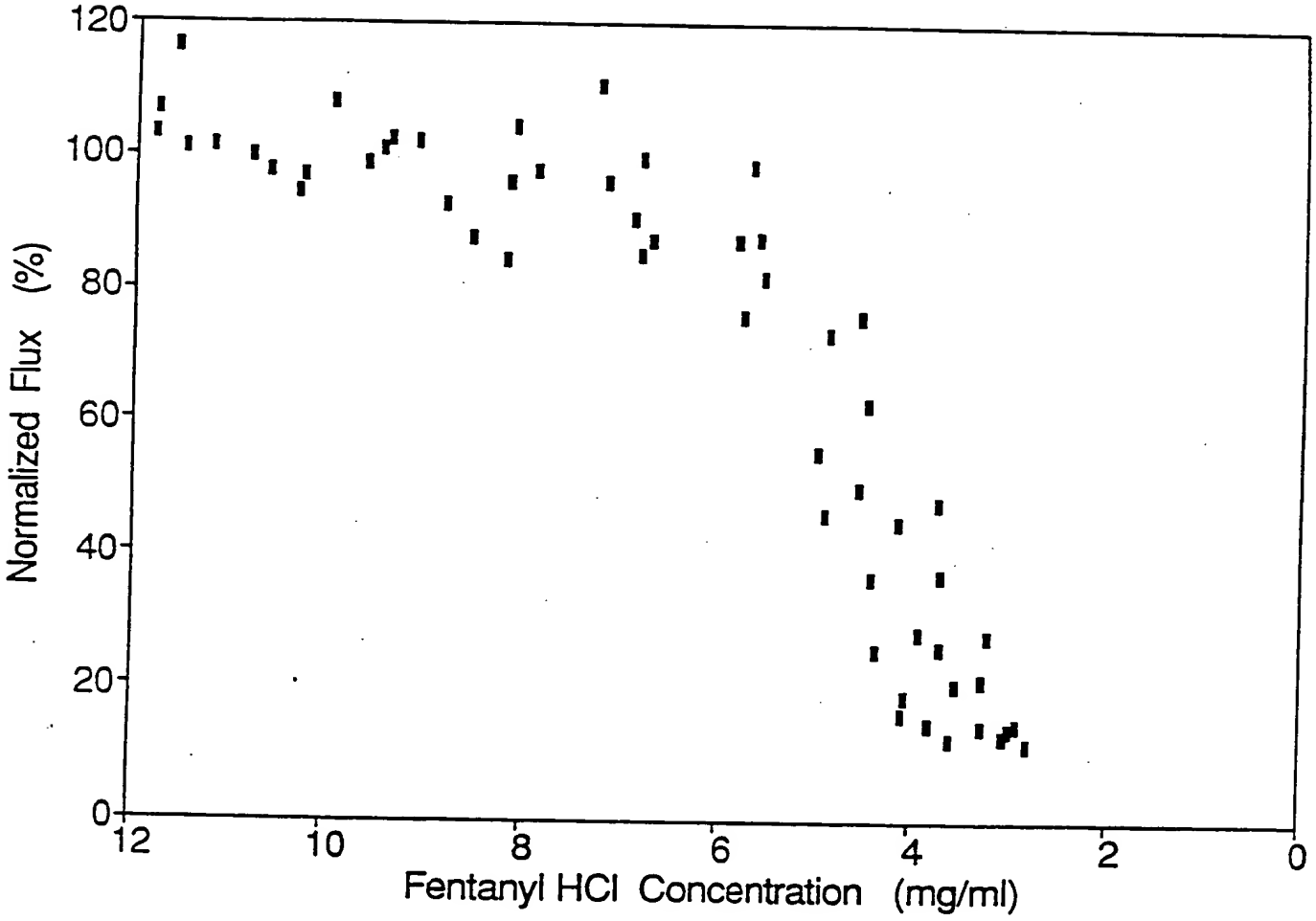

120
100
80
60
40
20
0
Normalized Flux (%)
12
10
8
6
4
2
0
Fentanyl HCl Concentration (mg/ml)

FIG. 2

APPENDIX D

Patent
Attorney's Docket No. 000951-089

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Joseph B. PHIPPS	)	Group Art Unit: 3306
	)	
Application No.: 08/463,904	)	Examiner: M. Bockelman
	)	
Filed: June 5, 1995	)	
	)	
For: METHOD AND DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL	)	

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Joseph Bradley Phipps, hereby declare that:

1. I am a citizen of the United States of America residing in Maple Grove, Minnesota.

2. I received my undergraduate degree in Materials Science from University of Utah and my doctorate in Materials Science from Northwestern University.

3. I have been employed by Alza Corporation since 1991 and my current title is Director of Research E-Trans Technology and my responsibilities include performing research in materials science and electrotransport devices, particularly waveform parameters such as voltage, current and timing to enhance biocompatibility and drug flux.

4. I am the inventor of the above-identified patent application and I have reviewed the Official Action dated March 10, 1997, and I am familiar with the prior art cited in the Action.

5. The cited prior art does not teach my invention and does not recognize the surprising discovery which I have made. In particular, it is important to recognize that fentanyl is an extremely potent analgesic that is approximately 100 times stronger than morphine and 5-10 times stronger than hydromorphone. Sufentanil is even more potent and is approximately 15 times stronger than fentanyl. With such potent drugs requiring only microgram quantities, there is always the danger of overdoses. Therefore, an electrotransport system for delivery of those potent substances must provide safe transdermal administration.

It was well known at the time of my invention that diffusion of fentanyl and sufentanil substances through the skin was possible without the application of current, especially if the system were inadvertently applied to a skin site with compromised barrier function (e.g., abraded, scratched, sunburned, etc.). It was also well known at the time of my invention that the rate of diffusion of a substance across the skin could be decreased by decreasing the drug concentration. Accordingly, low concentrations have been desired to minimize diffusion (i.e., passive delivery) when an electrotransport device is not transmitting current to the skin. Furthermore, it is desired that the donor reservoir contain only the amount of drug needed for treatment of the patient to minimize the potential for inadvertent misuse or abuse of a "used" system.

To demonstrate that the prior art does not teach my invention, I can refer to the article by R. V. Padmanabhan et al entitled "*In Vitro* and *In Vivo* Evaluation of Transdermal Iontophoretic Delivery of Hydromorphone", a copy of which is attached as Appendix A. The article describes experiments involving the iontophoretic delivery of hydromorphone hydrochloride and indicates the delivery rate was independent of the concentration of hydromorphone in the donor solution over the range from 0.01M to 0.8M and states on page 130:

> Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

In contrast to this teaching in the art, I have surprisingly found that the claimed concentrations of fentanyl and sufentanil in the donor reservoir are needed in order to achieve a drug flux that is independent of concentration for a given current. This discovery was especially surprising considering the research described in the Padmanabhan article, as well as the theoretical understanding existing at the time of my invention and to the present time. An often cited reference for the theoretical basis of electrotransport is the publication of G.B. Kasting and J.C. Keister entitled "Application of Electrodiffusion Theory For A Homogeneous Membrane to Iontophoretic Transport Through Skin", a copy of which is attached as Appendix B. The authors make theoretical predictions of the effect of donor drug concentration ~~drug concentration~~ on drug delivery efficiency (i.e., rate of drug delivery per unit current) for several cases. Their Case 1, beginning on page 202 develops the theoretical prediction for a drug salt with no added

JBC 6/6/97

NaCl in the donor reservoir and normal saline on the receptor side of the in vitro cell. On page 204, they conclude that, for this case:

> ...the efficiency of drug delivery is largely determined by the ratio of drug diffusivity in the skin to that of the predominant counterion on the opposite side of the membrane. It is independent of drug concentration in this example.

This stated conclusion assumes a primarily aqueous transport pathway through skin which was well established at the time of my invention.

Furthermore, rather than having a donor reservoir that is designed to be fully depleted when administration is completed, my invention requires the concentration to be maintained substantially throughout the delivery period which means that administration is terminated even though a substantial amount of the drug still remains in the reservoir. Therefore, I believe that my invention is not disclosed or suggested anywhere in the cited prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

June 6, 1997
Date

Joseph B. Phipps

Journal of Controlled Relea . . 1990) 123-135
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

IN VITRO AND *IN VIVO* EVALUATION OF TRANSDERMAL IONTOPHORETIC DELIVERY OF HYDROMORPHONE*

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Key words: transdermal drug delivery; iontophoresis; hydromorphone; narcotic; *in vivo* studies

The narcotic analgesic, hydromorphone, was delivered by constant-current iontophoresis from aqueous solution through excised pig and human skin and from a hydrogel formulation into domestic pigs. The delivery rate per unit current was found to be similar for both pig and human skin, with a value of 1.1 mg h^{-1} mA^{-1}, even though the passive fluxes differed by a factor of six. The in vitro *delivery rate through pig skin at a current density of 125 $\mu A/cm^2$ was found to be independent of the concentration of hydromorphone in the donor solution over the range from 0.01* M *to 0.8* M. *No correlation was observed between the initial passive hydromorphone delivery rate through pig skin and the steady-state rate during iontophoresis. In addition,* in vivo *delivery of hydromorphone into domestic pigs was studied at currents of up to 1.2 mA for 12 hours. Delivery rates were determined from plasma hydromorphone concentrations and from residual drug analysis of spent patches. The delivery rate per unit current determined from the plasma concentration and residual assay data were 1.9 and 1.2 mg h^{-1} mA^{-1}, respectively.*

INTRODUCTION

While there have been a number of investigations focusing on systemic iontophoretic drug delivery [1–4], few have attempted to compare *in vitro* and *in vivo* results [5–8]. Moreover, only a few investigators have studied iontophoretic delivery through various types of skin [5,6,9–11]. The goal of this study was to compare the *in vitro* transdermal iontophoretic delivery of hydromorphone through pig and human skin with *in vivo* delivery in the domestic pig.

In vitro steady-state delivery rates were determined by a standard flow-through cell technique. *In vivo* transdermal iontophoretic delivery of hydromorphone was performed at various currents and the steady-state rate determined by two methods. The first method compared the steady-state hydromorphone plasma concentration obtained during iontophoresis with the level observed during constant intravenous infusion in the same pig. The second method involved extraction of hydromorphone from hydrogel patches to determine the amount of drug lost during iontophoresis.

EXPERIMENTAL

During iontophoretic drug delivery, oxidation must occur at the anode. Several strategies

*Paper presented at the Fourth International Symposium on Recent Advances in Drug Delivery Systems, Salt Lake City, UT, U.S.A., February 21–24, 1989.

0168-3659/90/$03.50

have been adopted to minimize contamination of the drug reservoir with extraneous ions created at the anode during iontophoresis. One strategy is to buffer the donor medium to minimize pH changes caused by oxidation of water [12]; however, this results in reduced efficiency of drug delivery due to competition from extraneous ions [5]. Another strategy is to isolate the anode compartment from the drug reservoir by use of a salt bridge [13]. This method eliminates the need for a buffer but can lead to significant contamination of the drug reservoir if the test duration is long, particularly when the drug concentration or drug reservoir volume is small. Sanderson et al. [1,14] have described a system using an ion-selective membrane which minimizes cationic contamination of the donor compartment for cationic drugs. This technique is generally superior to the salt-bridge method but can still results in significant contamination of the drug reservoir.

The method used in this investigation has been previously described [5,6,9,10] and involves the use of a silver anode in direct contact with the donor medium. During iontophoresis, silver is oxidized and reacts with chloride ion (drug counter-ion) in the drug reservoir to form an insoluble silver chloride layer on the anode surface. This method prevents significant contamination of the drug reservoir for extended periods of time and is relatively easy to implement for *in vivo* studies.

In vitro delivery study

A two-compartment vertical glass diffusion cell (Skin Permeation Systems, Inc., Berkeley, CA) was used to determine the rate of hydromorphone delivery through excised skin as a function of current. A silver chloride cathode was placed in the receptor compartment (4 ml capacity) and a silver mesh anode in the donor compartment. Excised human or pig skin was placed on a Delrin® support fixture and clamped in place between the two compartments with the stratum corneum facing the donor compartment. The contract area between the donor solution and the excised skin was 8 cm^2. Pig skin was obtained from the mid-dorsal region of domestic, weanling pigs by dermatoming at a thickness of about 600 μm. Human skin was dermatomed at about 350 μm from the abdominal region of adult cadavers. Skin samples were stored frozen prior to use.

The jacketed receptor compartment was maintained at a temperature of 37°C by a circulating water bath and 0.1 *M* NaCl solution was pumped through the receptor chamber at a flow rate between 3 and 6 ml/h. The donor compartment was filled with 7 ml of hydromorphone hydrochloride (HMHCl) solution at concentrations from 0.01 *M* to 0.8 *M*. The anode and cathode were connected to a custom-built constant current power supply accurate to within 5% of the set-point value. Experiments were performed at currents of up to 2.0 mA for 24 hours.

In a typical experiment, a 0.1 *M* HMHCl solution was placed in the donor compartment for 18 hours prior to the application of current. This was done to insure that no leaks were present in the donor compartment prior to iontophoresis and to allow for determination of the passive hydromorphone flux through each skin sample. After 18 hours, the donor compartment was emptied, rinsed, and filled with fresh drug solution. A constant current was then applied for 24 hours followed by 24 hours of passive delivery. In some experiments the pre-iontophoretic passive phase and/or the post-iontophoretic passive phase were not performed.

During the 66 hour duration of a typical experiment, samples were collected continuously in two-hour intervals. The weight of each receptor sample was recorded and the hydromorphone concentration of selected samples was determined by HPLC using UV detection at 280 nm. A 5 nm C18 column (DuPont Instruments. Wilmington, DE) was used. The mobile phase was comprised of 59% 0.005 *M* heptane sulfonic

acid, 40% methanol, and 1% acetic acid and the flow rate was set at 1 ml/min.

Steady-state delivery rates were determined for each skin sample by multiplying the steady-state receptor concentration (achieved in approximately ten hours) by the receptor flow rate which was calculated from the weight of each 2-hour receptor sample. Average steady-state rates for each skin sample were calculated from five consecutive values observed between 12 and 24 hours after application of current.

Bioavailability study

The *in vivo* iontophoretic delivery system for hydromorphone was composed of two hydrogel electrode patches; a drug-loaded hydrogel patch and an "indifferent" hydrogel patch containing inorganic electrolytes. Both formulations were in direct contact with a metallic electrode mesh housed in a circular section of medical-grade polyethylene foam tape (Daubert, Inc., Chicago, IL). The hydrogel contact area of each patch with the skin was 25 cm^2. The drug-loaded patch had a silver mesh electrode and a hydrogel composed of 3.2% hydromorphone hydrochloride (Mallinckrodt, Inc., St. Louis, MO), 19% poly(vinyl alcohol) (DuPont), and 77.8% distilled water by weight. The indifferent patch had a chloridized silver mesh electrode and a conductive poly(vinyl alcohol) (PVA) hydrogel.

Six domestic weanling pigs weighing 8–12 kg were used in this study. Three treatments were given to each pig; iontophoretic delivery of hydromorphone at two different current levels and a third treatment of constant intravenous infusion of hydromorphone. Each iontophoresis experiment utilized a new dorsal skin site on the pig as well as new sets of electrode patches. All experiments were conducted over a period of approximately 12 hours. A wash-out period of approximately two days was allowed between treatments. Serial blood sampling was made possible by surgical placement of catheters in the jugular veins. For catheter placement, the pigs were anesthetized with 30 mg/kg Ketamine HCl intramuscularly.

Using electric clippers, hair on the dorsal surface of the pigs was carefully clipped and cleaned to eliminate surface debris. The hydrogel electrode patches were placed on the prepared skin sites and the appropriate lead wires from custom-built constant current power sources were connected to the drug-loaded and indifferent patches. The power sources, patches, and lead wires were all taped securely. Iontophoresis of hydromorphone was carried out at 0, 0.4, 0.8, and 1.2 mA for periods of up to 12 hours.

The infusion studies involved continuous and constant intravenous delivery of hydromorphone at a rate of 1 mg/h. Blood samples in both iontophoresis and infusion experiments were collected at predose and hourly for 12 hours. Plasma concentrations of hydromorphone were measured using a HPLC assay with electrochemical detection [15].

Drug residue study

The iontophoretic patches used in this study consisted of a PVA-based hydrogel pad containing 1% by weight hydromorphone hydrochloride (50 mg HMHCl content) in contact with a silver mesh electrode and held in place on the skin by an adhesive polyethylene foam housing. A conductive indifferent hydrogel housed in a similar manner, but in contact with a chloridized silver electrode, was spaced 2.5 cm from the drug-loaded hydrogel. The skin contact area was 14 cm^2.

Patches were placed on the dorsal surface of 28 domestic pigs weighing about 10 kg and constant currents of 0.25 mA ($n=5$), 0.50 mA ($n=11$), and 0.75 mA ($n=12$) were maintained for 12 hours. Patches were removed after iontophoresis, sealed in polyethylene bags, and refrigerated prior to drug extraction. Each drug-loaded hydrogel was removed from its housing, immersed in an aqueous codeine phosphate so-

TABLE 1

Conditions used in gradient elution HPLC of extracts (5 μm Supelcosil LX-C_{18}-DB column)

Mobile Phase: A:	1% acetic acid, pH 4.0							
B:	70/30, acetonitrile/water							
Gradient program:	Time, min.:	0	5	10	22	27	28	34
	% B.:	5	10	10	50	50	5	5
Detection wavelength:	280 nm							
Flow rate:	2 ml/min							
Column temperature:	40°C							
Injection volume:	40 μL							

lution (used as an internal standard), and agitated for a minimum of sixteen hours at room temperature. Aliquots of the extract were analyzed by a gradient elution HPLC method to ensure separation of any impurities from the analyte of interest. A 5 μm Supelcosil LC-C_{18}-DB column (Supelco, Inc., Bellefonte, PA) was employed; the chromatographic conditions used are shown in Table 1.

RESULTS AND DISCUSSION

In vitro delivery study

In vitro delivery experiments using aqueous hydromorphone hydrochloride solutions were performed as a function of current, drug concentration and skin type. Table 2 compares the average-state delivery rates of hydromorphone through pig and human skin at currents of 0, 0.5, and 1.0 mA (i.e., current densities of 0, 63, and 125 μA/cm^2). Two passive rates from 0.1 *M* HMHCl solution are given for each type of skin. The first rate (designated "a") is a steady-state value and was measured at the 16–18 hour interval following introduction of the donor solution. The second steady-state rate (designated "b") was observed during the 22–24 hour interval after termination of ionthophoretic delivery of hydromorphone at 1 mA for 24 hours.

For pig skin, the average passive rates before and after iontophoresis were nearly equal, suggesting that the current had little effect on skin permeability, as measured by this method. However, a significant decrease in the magnitude of the standard deviation was observed after iontophoresis. A closer examination of 14 matched pairs of passive rates (i.e., before compared to after) revealed that most skin samples with rates below the mean before iontophoresis had larger passive rates after iontophoresis, while most samples with large initial passive rates had smaller rates after iontophoresis. The passive rates for the five skin samples with the smallest initial values increased by an average of 67% from 88 ± 36 μg/h before iontophoresis to 148 ± 26 μg/h after iontophoresis. In contrast, the passive rates for the four skin samples with the largest intial values decreased by an average of 38%, from 398 ± 19 μg/h before iontophoresis to 247 ± 40 μg/h after iontophoresis. In summary, the application of current tended to homogenize passive transport of hydromorphone through pig skin.

TABLE 2

A comparison of the average steady-state delivery rates for pig and human skin at currents of 0, 0.5, and 1.0 mA (n = number of skin samples)

Current (mA)	Average steady-state rate (μg/h)			
	Pig skin		Human Skin	
	n	Rate ± SD	n	Rate ± SD
0	137[a]	205 ± 163	20[a]	2 ± 6
	14[b]	216 ± 74	9[b]	33 ± 25
0.5	5	566 ± 82	8	573 ± 145
1.0	19	1150 ± 159	9	1053 ± 172

[a]Pre-iontophoretic value
[b]Post-iontophoretic value.

An explanation for this observation may be that the ionic current created new hydromorphone pathways in the least permeable skin samples while "plugging" fast ionic transport pathways in the more permeable skin samples. Burnette [16] has cited evidence to support the

presence of at least two ionic pathways through skin: one via pores and the other through the intercellular region of the stratum corneum. He suggested that the intercellular pathway may become more important as the skin hydrates during iontophoresis. Hydration of the polar head group region of the lipid bilayer and/or the corneocyte–bilayer interface may provide such ionic pathways. Burnette also noted that pores present in the skin may narrow due to tissue hydration during iontophoresis. If true, this narrowing of pores could result in smaller passive fluxes for hydromorphone after iontophoresis for those skin samples which initially had large cross-sectional pore areas and therefore large pre-iontophoretic passive fluxes. The application of current may cause the pores to become less permeable to ionic hydromorphone while increasing the permeability of the intercellular pathway. Based on this interpretation, the effect of iontophoresis on the passive delivery of hydromorphone would be determined by the density of pores present in the skin. The dual pathway model suggested by Burnette is consistent with the passive flux data for pig skin; however, a larger data set is required for verification.

The average passive rates before and after iontophoresis for human skin are also listed in Table 2. Of the twenty skin samples for which initial passive rates were measured, only one had a measurable rate after 18 hours of exposure to 0.1 *M* HMHCl. In nine of these twenty skin samples, a steady-state passive rate was also measured in the 22–24 hour period following iontophoresis at 1 mA for 24 hours. For eight of these human skin samples, a passive rate was measurable after iontophoresis. One may be tempted to conclude that the permeability of human skin was altered by the application of current thus leading to an increased passive flux. However, in one human skin sample, where passive delivery was maintained for a 66 hour period, a steady-state passive flux was not achieved until 22 hours after introduction of the donor solution. Because human skin is less permeable to hydromorphone ions than pig skin, greater time may be required to saturated the skin and so passive steady-state delivery may not be achieved as quickly as with pig skin. Based on the pig skin data, the pre-iontophoretic passive flux for human skin may have become similar to the post-iontophoretic steady-state value had sufficient time been allowed for skin saturation. A comparison of the post-iontophoretic passive data listed in Table 1 for pig and human skin indicates that pig skin was about six times more permeable to hydromorphone ions than human skin.

Even though human skin was much less permeable to hydromorphone ions than pig skin, the average steady-state delivery rates at 0.5 and 1.0 mA were very similar as shown in Table 2. This result is in agreement with previous studies with pyridostigmine [6] where even though the passive delivery rate through mouse and human skin differed by a factor of ten, the iontophoretic rates were found to be very similar. As a general rule, the use of constant current iontophoresis tends to equalize the drug delivery rate through different types of skin, provided that passive drug delivery is a small contribution to the total delivery rate.

The distribution of passive rates for 137 pig skin samples prior to iontophoresis is given in Fig. 1. About forty percent of the values were less than 120 μg/h, with another forty percent between 120 μg/h and 320 μg/h. For comparison, the distribution of steady-state rates observed through 19 pig skin samples (four steady-state values per sample) during iontophoresis at a current of 1 mA is given in Fig. 2. In this case forty-five percent of the values were between 960 μg/h and 1080 μg/h and thirty-two percent between 1080 μg/h and 1320 μg/h. The similarity in the passive and iontophoretic distributions may suggest that the variability present in the passive flux data is reflected in the iontophoretic data. However, no correlation ($r^2=0.1$) between the passive and iontophoretic rates was observed for the 14 pig skin samples where matched data was available. This

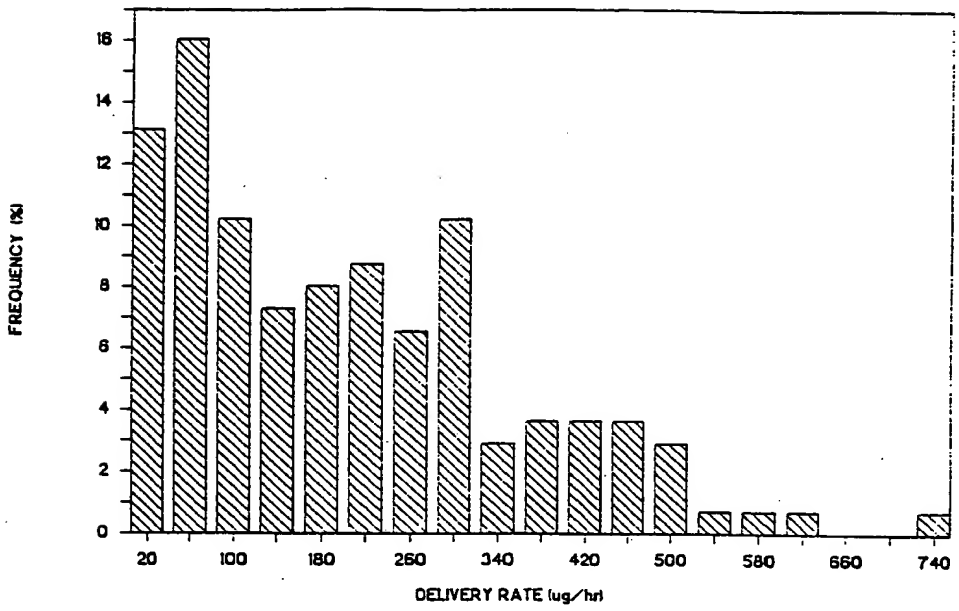

Fig. 1. Distribution of passive steady-state delivery rates from a 0.1 *M* HMHCl aqueous solution through pig skin (8 cm^2, $n = 137$).

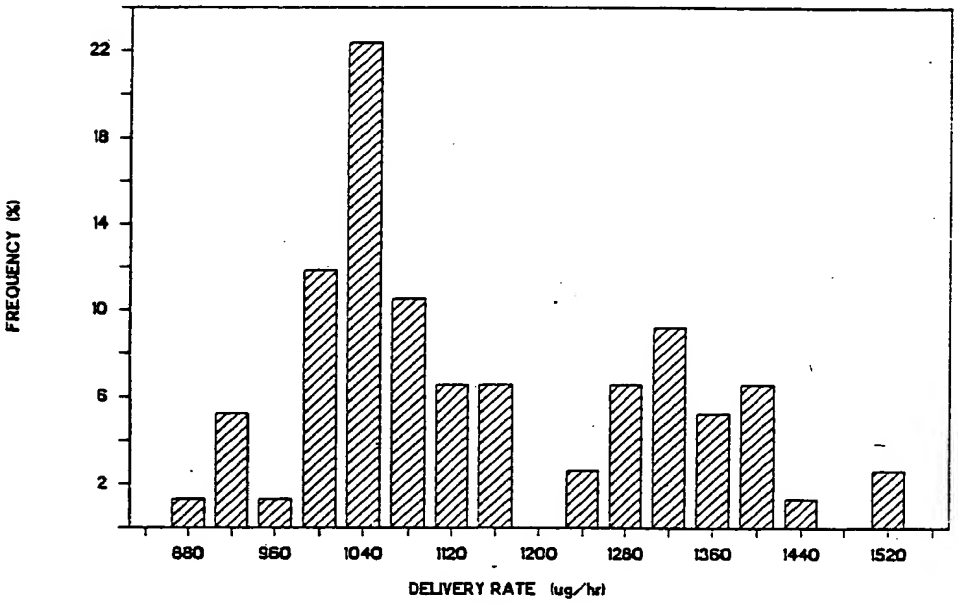

Fig. 2. Distribution of iontophoretic steady-state delivery rates from an 0.1 *M* HMHCl aqueous solution through pig skin at 1 mA (8 cm^2, $n = 19$).

result suggests that the passive permeability of skin does not directly influence the delivery rate during constant current iontophoresis.

Figure 3 plots the average steady-state rate as a function of current for delivery from a 0.05 *M* HMHCl solution through pig and human skin. A linear dependence of rate on current is clearly evident as is the similarity of the deliv-

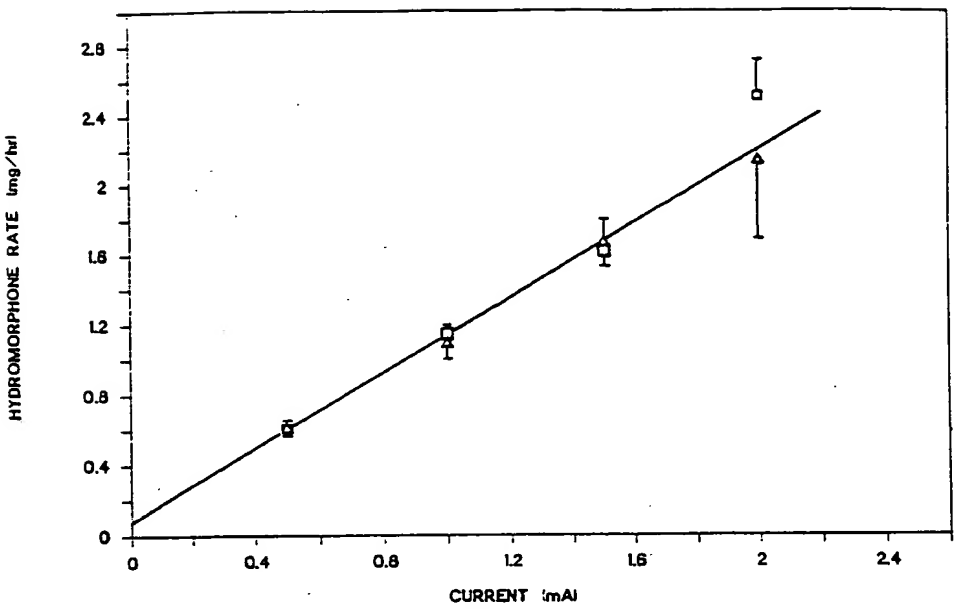

Fig. 3. Comparison of the average steady-state delivery rates of hydromorphone through pig (△, $n=5$) and human (□, $n=9$) skin from a 0.05 M HMHCl aqueous solution, as a function of current. The line is a linear regression fit of the pig skin data. Error bars indicate one standard deviation.

ery rate at each current for the two types of skin. The slope of the linear dependence, S, was used to calculate the efficiency of drug delivery, E_d, from the expression

$$E_d = SF/M_w$$

where M_w is the molecular weight of the drug ion and F is Faraday's constant [5,6,12,17]. The efficiency of drug delivery is a measure of the molar quantity of drug transported across the skin per unit time for each faraday of charge supplied by the power source per unit time. The slopes calculated from linear regression analysis were 1.1 mg h^{-1} mA^{-1} for pig skin and 1.2 mg h^{-1} mA^{-1} for human skin. The efficiency of hydromorphone delivery through the skin calculated from these values was 0.11 which is less than the free solution value of 0.18. Therefore, only 11% of the total ionic charge crossing the skin was carried by hydromorphone ions.

To determine if the hydromorphone concentration of the donor solution affects the rate of delivery across skin, several experiments using pig skin were conducted at 1 mA with hydromorphone solutions ranging from 0.01 M to 0.8 M in concentration. The steady-state data are summarized in Table 3. No significant difference in steady-state rate was observed over this broad concentration range. While no experiments were performed at concentrations less than 0.01 M, it should be noted that steady-state delivery of hydromorphone from the 0.01 M solution was maintained for approximately 16

TABLE 3

A comparison of the average steady-state delivery rates through pig skin from aqueous hydromorphone HCl solutions at different concentrations (n=number of skin samples)

Drug concentration (mM)	n	Average steady-state rate (μg/h) ± SD
10	3	1049 ± 183
30	3	1269 ± 43
100	19	1150 ± 159
400	3	1118 ± 180
800	3	1000 ± 71

hours. Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

The delivery rate of hydromorphone through pig skin due to an applied current is proportional to the concentration of hydromorphone in the skin as determined by the partition coefficient, the donor solution concentration, and the voltage drop across the donor solution–skin interface [16]. In this study partitioning of hydromorphone ions into the skin was not affected by the bulk donor solution concentration suggesting that the hydromorphone activity at the solution/skin interface was held constant during iontophoresis. The free solution hydromorphone transport number (0.18) was found to be greater than the transport number through the skin (0.11), which implies that the quantity of hydromorphone migrating to the skin surface was greater than the quantity transported through the skin during iontophoresis. Therefore, the hydromorphone concentration at the skin will be greater than the bulk solution value during iontophoresis. This phenomenon may be responsible for the lack of dependence of the transdermal delivery rate on the bulk solution concentration. The results of this study are contrary to those of Miller and Smith [13] where a concentration-dependent flux was observed for acetate ions.

In vivo studies

In addition to the *in vitro* investigation, two *in vivo* studies were performed; a six-pig bioavailability study and a 28-pig drug residue study. In the six-pig bioavailability study, apparent steady-state plasma levels were evident during the 12-hour period for both iontophoretic and infusive delivery of hydromorphone. This was true in all cases except for that involving intravenous infusion in one pig. In all other animals a steady-state plasma concentration was observed over the period of 4–12 hours. Hydromorphone was not detected in the plasma for those pigs in which no current was applied

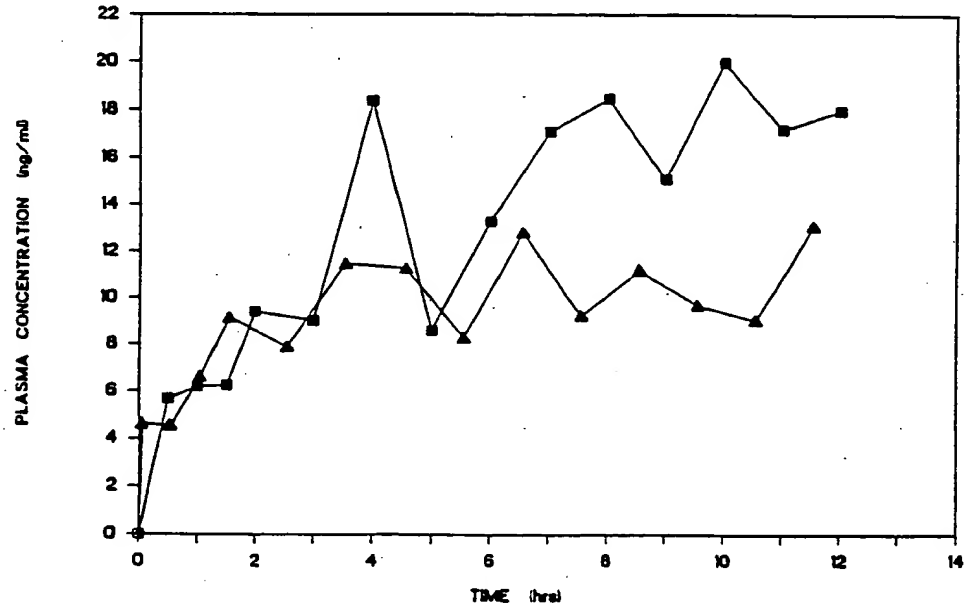

Fig. 4. Plasma hydromorphone concentrations observed during transdermal iontophoresis at 0.8 mA (■) and intravenous infusion at 940 μg/h (▲) for Pig B.

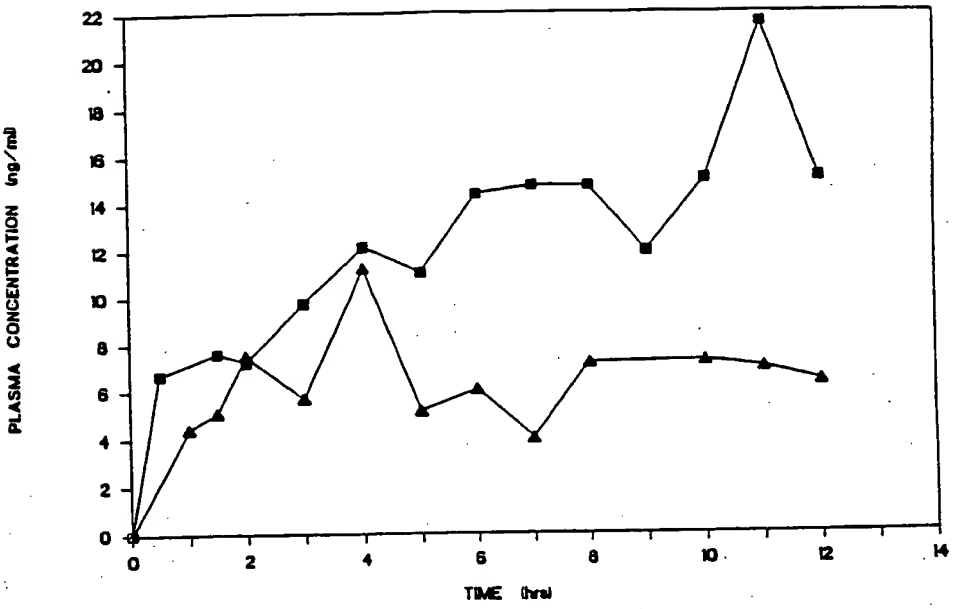

Fig. 5. Plasma hydromorphone concentrations observed during trandermal iontophoresis at 1.2 mA (■) and intravenous infusion at 950 μg/h (▲) for Pig F.

to the iontophoretic patch (passive condition, $n=3$).

A comparison of the plasma concentration as a function of time during transdermal iontophoresis and IV infusion is provided in Figs. 4 and 5 for Pigs B and F. A similarity in the plasma concentration profiles for these two delivery methods is evident. The "lag phase" often observed during passive transdermal drug delivery was not observed during transdermal iontophoretic delivery of hydromorphone.

The average steady-state hydromorphone levels were calculated as the area-under-the-curve over the 4–12 hour period, divided by the length of this interval, and are summarized in

TABLE 4

A summary of the total body clearances for six pigs as calculated from the infusion rates and steady-state plasma concentrations (eqn. 1)

Pig	Infusion rate (μg/h)	Steady-state plasma concentration (μg/L)	Total body clearance ($L\,h^{-1}kg^{-1}$)
A	949	7.95	12.8
B	942	10.50	10.2
C	1000	6.39	16.7
D	969	12.00	7.7
E	902	NA	11.8[a]
F	949	6.61	11.4

[a]Plasma clearance of hydromorphone was taken as the mean value determined from the other five animals.

TABLE 5

A summary of the iontophoretic delivery rates for currents of 0.4, 0.8, and 1.2 mA as calculated from eqn. (2)

Current (mA)	Pig	Steady-state plasma concentration (μg/L)	Iontophoretic delivery rate (μg/h)
0.4	D	5.23	422
	E	5.24	516
	F	2.59	373
0.8	A	9.92	1180
	B	16.00	1430
	C	12.52	1950
1.2	D	14.14	1140
	E	31.42	3100
	F	14.66	2110

Table 4 for the infusion experiments and Table 5 for the iontophoretic experiments. The total body clearances of hydromorphone for each pig are also listed in Table 4 and were calculated from the average steady-state plasma concentrations $\bar{C}_{ss(inf)}$, according to the equation

$$TBC = k_o/\bar{C}_{ss(inf)} \quad (1)$$

The iontophoretic delivery rate of hydromorphone, R_{ion}, was calculated using the expression

$$R_{ion} = TBC \cdot \bar{C}_{ss(ion)} \quad (2)$$

where $\bar{C}_{ss(ion)}$ is the average-state level of hydromorphone. These values are given in Table 5 and plotted as a function of current in Fig. 6. It should be noted that since the results from Pig E during the constant-rate infusion were inconclusive, no estimate of this pig's clearance was possible. The clearance of hydromorphone in Pig E was therefore estimated to be the mean of value for the other five pigs in the study.

Based on the results from the *in vitro* phase of this study, a linear relationship between the rate of iontophoretic delivery and current was assumed, and linear regression analysis assuming equal weighting of the data was performed. The equation which describes the relationship was found to be

$$R_{ion}\ (\mu g/h) = 1860I - 97 \quad (3)$$

where I is the current in milliamperes ($r^2 = 0.77$).

It can be seen from the data in Table 4 that there is a significant degree of variation in the plasma concentrations for the infusion experiments. Hydromorphone was infused at a constant rate of approximately 1 mg/h in all six animals; however, the weight range in the animals was from 8.35 to 12.6 kg. In most instances the variation in steady-state plasma levels is reduced when the infusion rates were normalized based on body weight.

The normalized plasma clearances for hydromorphone averaged 11.8 L h^{-1} kg^{-1} body weight. Little information is available in the literature concerning the hepatic blood flow in weanling pigs although reference to a blood flow in adult pigs weighing 76 kg was found to be approximately 2.7 L h^{-1} kg^{-1} [18]. The present study involved the analysis of hydromor-

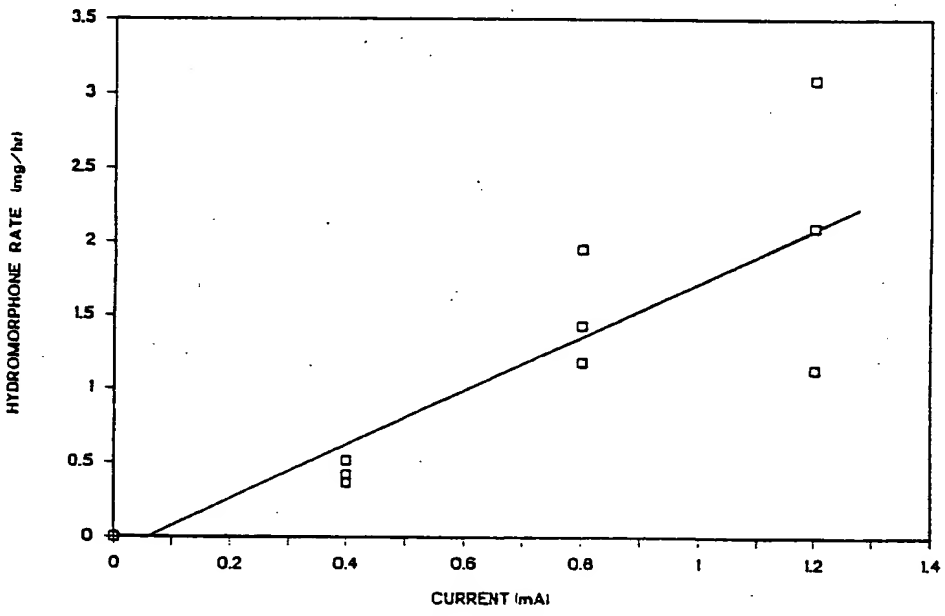

Fig. 6. The steady-state delivery rate of hydromorphone from 3.2% HMHCl hydrogels into weanling pigs as a function of current. The skin contact area was 25 cm^2.

TABLE 6

Average loss of hydromorphone from hydrogels after iontophoresis for 12 hours at three currents (n = number of patches)

Current (mA)	n	Average drug loss (mg) ± SD
0.25	5	4.4 ± 0.3
0.50	11	8.9 ± 2.7
0.75	12	11.9 ± 1.5

phone in plasma rather than whole blood, and no information is presently available concerning the distribution of hydromorphone between plasma and erythrocytes in the pig. It is therefore difficult to assess this apparently high plasma clearance in terms of literature values for hepatic blood flow, although the calculated figures do seem to be high. It should be noted that this uncertainty stems from the results of the intravenous infusion experiments, and should not invalidate conclusions drawn from the results of the iontophoretic delivery studies since the calculation of R_{ion} involves relative steady-state levels ($C_{ss(ion)}/C_{ss(inf)}$).

Determination of the iontophoretic delivery rates as the product of the average steady-state concentrations and the clearances calculated from the infusion studies assumes that clearance was concentration independent. In other words, linear elimination kinetics were assumed in the analysis of the data. From the data in Table 5, there is a suggestion of a disproportionate increase in the iontophoretic delivery rate as the current increases, particularly at low current levels. This observation can be explained by a nonlinearity either in the elimination of hydromorphone, or in the delivery of the drug by iontophoresis. The *in vitro* data would favor the former explanation since the *in vitro* delivery rate was linearly dependent on current (Fig. 3). If there is nonlinear clearance of the drug in the pig (i.e., the clearance decreases at higher concentrations of hydromorphone) the apparent nonlinearity would not be associated with the iontophoretic delivery method but rather with the clearance of the drug. Further studies would be required to ex-

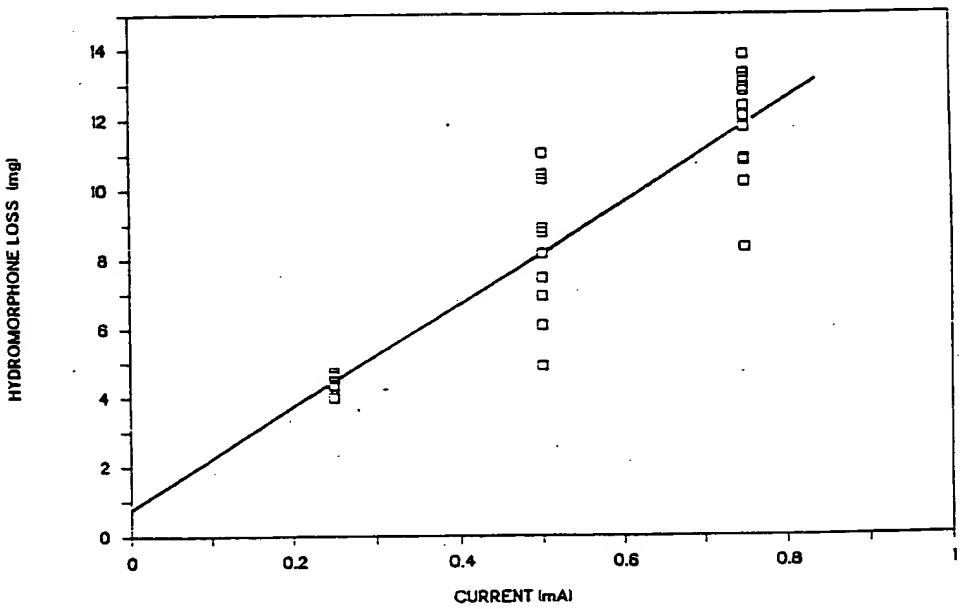

Fig. 7. The amount of hydromorphone lost from 1% HMHCl hydrogels after 12 hours of iontophoresis at currents of 0.25, 0.50, and 0.75 mA. The skin contact area was 14 cm^2.

TABLE 7

Comparison of delivery rate per unit current calculated from linear regression analysis of *in vitro* and *in vivo* data

Data source	Slope ($mg\ h^{-1}\ mA^{-1}$)
In vitro/Pig skin	1.07 ± 0.15
In vivo/Drug residue	1.23 ± 0.18
In vivo/Plasma concentration	1.86 ± 0.32

amine this possibility more closely in a larger population of animals.

In another *in vivo* study, hydromorphone was delivered to 28 pigs for 12 hours from a hydrogel formulation containing 1% by weight HMHCl. The skin contact area was 14 cm^2 and the currents employed were 0.25 mA ($n=5$), 0.50 mA ($n=11$), and 0.75 mA ($n=12$). Following iontophoresis, the hydromorphone content of each hydrogel was determined. The average drug lost at each current is summarized in Table 6. Figure 7 is a plot of the hydromorphone lost from each hydrogel as a function of current and the line shown in a linear regression fit to the data ($r^2=0.77$). The slope of this line was used to estimate the iontophoretic delivery rate per unit current which is compared to the values determined from the *in vitro* study (slope of data in Fig. 3) and the bioavailability study (eqn. 3) in Table 7.

Considering the diversity of the techniques employed, the agreement between the *in vitro* and *in vivo* data is good. However, the delivery rate per unit current calculated from the bioavailability data is significantly larger than the values estimated from the *in vivo* drug residue study and the *in vitro* data. This may indicate that the total body clearances used to calculate the *in vivo* delivery rates were an overestimate of the true values, possibly due to nonlinear elimination kinetics of hydromorphone in the pig.

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Review

APPLICATION OF ELECTRODIFFUSION THEORY FOR A HOMOGENEOUS MEMBRANE TO IONTOPHORETIC TRANSPORT THROUGH SKIN

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Two simple models for ionic mass transport across membranes are discussed in the context of iontophoretic delivery of drugs through skin. The constant field model is mathematically the most tractable and offers some insights into the time dependence of iontophoretic transport. However, for thick membranes or for systems in which the total ion concentrations on opposite sides of the membrane differ appreciably, the electroneutrality approximation is more appropriate. Since both of these conditions are likely to be found in skin iontophoresis studies, the electroneutrality model should provide a better starting point for analyzing the details of iontophoresis experiments than does the constant field model. Equations for the diffusion potential, ion transference numbers and partition coefficients and the current–voltage characteristic of the membrane are given, enabling one to calculate ionic fluxes and active/passive flux ratios for a given applied current or voltage. As an example, the flux and transference number of a monovalent drug ion driven across a membrane in the presence of sodium chloride are calculated. Finally, known discrepancies between the predictions of the homogeneous membrane models and available experimental data are examined, and suggestions are made for modifying the theory to resolve these differences.

INTRODUCTION

Solutions to the Nernst–Planck flux equations have been used for many years to describe the potentials which develop across biological and synthetic membranes in the presence of ion gradients. Two of the most useful approximate solutions are those of Planck himself [1] and of Goldman [2]. Planck made the assumption that all points within the membrane were electrically neutral on a microscopic scale and arrived at an analytical solution for the steady-state ion concentrations, fluxes, and membrane potential for the case of 1:1 electrolytes. Schlögl [3] later extended this approach to include more complex electrolyte mixtures. Goldman, on the other hand, assumed that the electric field was everywhere constant, leading to a solution which is applicable to ions of any valence. We recently showed that the time-dependent Goldman problem has an analytical solution with a simple closed form at steady state [4]. The solution can be used to calculate the flux and the time lag for ionic transport in cases where the constant field assumption is appropriate.

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The range of validity of the Planck and Goldman approximations in biological systems has received considerable discussion [5–8]. Essentially, the Planck approximation fails for very thin membranes in which surface charge layers extend an appreciable distance into the membrane. The Goldman approximation, on the other hand, fails when the membrane is thick or when the total ion concentrations on opposite sides of the membrane differ appreciably. When these concentrations are exactly equal, the two approximations lead to the same result for both ionic fluxes and membrane potentials.

In the case of iontophoresis of drugs through skin, the membrane with which one is dealing is the stratum corneum or, perhaps, the set of shunts through the stratum corneum provided by sweat ducts and hair follicles. A complete solution to the problem of drug transport may have to include the effect of skin heterogeneity, the effect of fixed charges and convective coupling between flows, and contributions from more than one pathway and more than one drug species (if the pK_a of the drug is in the vicinity of the skin pH). Furthermore, the transport properties of the membrane (i.e., ion mobilities or diffusivities) may change upon application of appreciable electrical currents or potentials across the membrane. Nevertheless, in order to understand how the behavior of skin under iontophoresis differs from that of an ideal membrane, one must first understand ideal behavior. This, in itself, can be quite complex. The purpose of this paper, therefore, is to review the process of driving ions across a homogeneous membrane in contact with two electrolyte solutions. To avoid undue complexity, the discussion will be limited to uncharged membranes and 1:1 electrolytes, e.g., (Na,K)Cl or $MgSO_4$. The monovalent ion case should be applicable to singly ionized drugs driven through a membrane into a physiologic medium, where the polyvalent ion concentration is low. We will, in addition, discuss the form of ion partitioning at the membrane-solution interface when the membrane is oily or lipophilic in nature and the system is at or near equilibrium. The electroneutrality model presented here should serve as a better starting point for describing ionic flow through skin than the constant field approach since (1) the skin is thick relative to bilayer membranes; (2) topically applied drugs are likely to be applied in widely varying concentration; and (3) oil–water partitioning effects are accounted for in the model.

We wish to emphasize the words "starting point" when discussing the homogeneous membrane models presented below. The writers are aware that some of the predictions of these models are controverted by data already in the literature [9–13]. It was, in fact, our own frustrations with trying to explain the observed iontophoretic enhancements with EHDP, a negatively charged bone resorption agent, that first led us to a closer examination of these equations [13,14]. Although more complex models will undoubtedly be required to explain these data, our intention here is to establish the framework about which such models may be built.

These approximate solutions to the Nernst–Planck equations have been in use for a long period of time. However, much of the attention of earlier workers was devoted towards analyzing the spontaneous membrane potentials or liquid junction potentials which arise from independently maintained ion gradients. While these so called "diffusion potentials" are still of importance to iontophoretic transport, the emphasis here is to predict the ion current (and, hence, ionized drug flux) which results when an external potential is imposed across a membrane. The resulting equations have a form which is not commonly found in the earlier literature.

THEORY

The steady-state flux J_i of an ion through a convection-free fluid in the presence of an electric field E is governed by the Nernst–Planck flux equation for that ion:

$$J_i = -D_i\frac{dc_i}{dx} + \frac{D_i z_i e E c_i}{kT} \qquad (1)$$

where D_i is the diffusion coefficient for the ion, z_i is its charge, c_i is its concentration, and kT is the thermal energy of the system. For simplicity we restrict the problem to the x dimension. When multiple ions are present, the flux of each must satisfy an equation of the form shown in eqn. (1). In addition, Poisson's equation must be satisfied at all points in the system:

$$d^2\phi/dx^2 = \rho(x)/\epsilon \qquad (2)$$

where $\phi = -\int E dx$ is the electrical potential, ϵ is the permittivity of the material and $\rho(x) = e\sum_i z_i c_i$ is the space charge density. In simple membranes where carrier systems and coupling between flows may be neglected, eqns. (1) and (2) plus boundary conditions on the c_i and ϕ on the two sides of the membrane completely specify ionic transport.

Let us assume that both sides of a membrane are in contact with a well-stirred fluid electrolyte. The electrical potential and ionic concentrations in the two solutions then determine the boundary conditions for membrane transport. If there are no significant partition equilibria between the solution and the membrane (e.g., a "water" membrane bathed in aqueous solutions), then the concentrations and potential just inside the membrane surfaces are identical to those in the solutions with which they are in contact. Examples of this type of membrane include the microporous membranes used for dialysis and ultrafiltration and, possibly, the appendageal pathways through skin.

If, on the other hand, the composition of the membrane differs significantly from that of the solutions (e.g., an oil membrane bathed in aqueous solutions), then ionic concentrations and electrical potential will change abruptly at the two interfaces. These changes arise from differences in the standard state free energy of ions in the oil and water phases. Assuming that the partition equilibria are established rapidly compared to transport through the membrane, the ionic partition coefficients and the potential jump at the interface can be calculated by equating the free energy of each species in the two phases. The relevant equations are [5]:

$$\mu^\circ_{i,s} + RT\ln c_{i,s} + z_i F\phi_s = \mu^\circ_{i,m} + RT\ln c_{i,m} + z_i F\phi_m \qquad (3)$$

where a separate equation applies to each species at each interface. Here the subscript s refers to the solution phase, m to the membrane phase, $\mu^\circ_{i,y}$ is the standard state free energy of species i in phase y and F is the Faraday constant (96,500 coulomb/mol). We consider all solutions to be ideal; otherwise, the concentrations $c_{i,s}$ and $c_{i,m}$ should be replaced by activities $a_{i,s}$ and $a_{i,m}$. The quantity

$$\Delta\phi_{sm} = \phi_m - \phi_s \qquad (4)$$

is known as the phase boundary potential. Since there are two interfaces in a membrane transport problem, there are two phase boundary potentials to be considered. If the composition of the solutions on the two sides of the membrane is identical, then the two boundary potentials cancel; otherwise, a net differential will exist and should be considered when calculating the potential drop across the membrane. This is likely to be the case when a drug solution is placed in contact with stratum corneum, which (except for the pores) may be considered to be a lipoidal barrier [15].

If the D_i are known and boundary conditions are specified, eqns. (1)–(3) can in principle be solved to yield the fluxes, electric field, and concentration profiles within the membrane. The exact solution must usually be obtained numerically, since the equations are nonlinear. The Planck and Goldman approximations offer two ways of obtaining analytical solutions to eqn. (1) by approximating eqn. (2) in different ways.

Constant field model (Goldman approximation)

Consider the situation shown in Fig. 1. A homogeneous membrane of thickness h separates

two well-stirred solutions, each containing M cations with concentrations c_i and N anions with concentrations $\bar{c}_k$. A potential $\Delta\phi=\phi_h-\phi_0$ is either applied or develops spontaneously across the membrane. The partition coefficient for each species at the membrane-solution interface is for the moment assumed to be unity.

The Goldman approximation consists of setting $\rho(x)=0$ in eqn. (2), which leads to $E(x)=-\mathrm{d}\phi/\mathrm{d}x=\text{constant}=-\Delta\phi/h$. Substituting this value for E into eqn. (1), integrating, and applying boundary conditions yields [2,4]:

$$J_i=\frac{-D_i\nu}{h}\frac{c_{ih}-c_{i0}\exp(-\nu)}{1-\exp(-\nu)} \tag{5}$$

where c_{i0} and c_{ih} are the concentrations of the ith species at the boundaries of the membrane and ν is a dimensionless driving force given by:

$$\nu=z_i e\Delta\phi\ /kT \tag{6}$$

An identical equation holds for the negative ions. The flux for each species is independent of the concentration of other ions in the solution, and the equation is applicable for all values of z_i. The total electric current which passes through the membrane is:

$$I=\sum_i J_i z_i F+\sum_k J_k z_k F \tag{7}$$

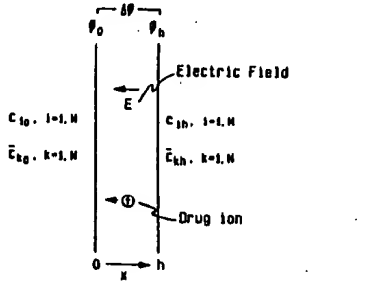

Fig. 1. Model for iontophoretic transport in a homogeneous membrane. If ϕ_h is made positive with respect to ϕ_0, the electric field E will have the direction shown and positive ions will be driven from right to left (and negative ions from left to right). In this problem, there are M positive species and N negative species.

In the absence of an applied field, a spontaneous potential known as the diffusion potential, $\Delta\phi_0$, develops across the membrane. It may be calculated by setting $I=0$ in eqn. (7). The result is [7]:

$$\Delta\phi_0=\frac{kT}{e}\ln\left(\frac{U_0+V_h}{U_h+V_0}\right) \tag{8}$$

where $U=\sum_i D_i c_i$ and $V=\sum_k D_k\bar{c}_k$. For the case of a species which is present only on the "donor" side of the membrane, $x=h$ (i.e., a hypothetical drug permeant), the flux ratio at applied voltage $\Delta\phi$ versus that with the voltage clamped at zero is:

$$\frac{J(\nu)}{J(0)}=\frac{\nu}{1-\exp(-\nu)} \tag{9}$$

Since a diffusion potential is generally present during a passive diffusion experiment involving this permeant, the active/passive flux ratio is not given by eqn. (9), but by $J(\nu)/J(\nu_0)$, where ν_0 is calculated from eqns. (6) and (8) with $\Delta\phi=\Delta\phi_0$ and $J(\nu)$ and $J(\nu_0)$ are separately calculated from eqn. (9).

Further development of this model, including the time dependence into the problem, leads to a related expression for the time lag to achieve steady state flux [4]. The result is:

$$\frac{t_L(\nu)}{t_L(0)}=\frac{6}{\nu^2}[\nu\coth(\nu/2)-2] \tag{10}$$

where $t_L(0)=h^2/6D_i$ is the familiar result from passive diffusion. (As with the flux ratio, the observed time lag ratio is actually $t_L(\nu)/t_L(\nu_0)$.) Equation (10) shows that substantial reductions in the time required to initiate or terminate transdermal drug delivery are possible via iontophoresis.

Electroneutrality approximation (Planck assumption)

The situation described in Fig. 1 is assumed to hold. Planck's approximation consists of substituting the electroneutrality condition

$$\sum_{i=1}^{M} z_i c_i+\sum_{k=1}^{N} z_k\bar{c}_k=0 \tag{11}$$

for eqn. (2) and then simultaneously solving eqn. (1) for all species with this constraint. The general solution is quite tedious; however, for the case of a 1:1 electrolyte and an uncharged membrane, the total ion concentration profile across the membrane is linear and the solution is relatively straightforward. An outline of the solution is given in Appendix 1. The resulting steady state flux is:

$$J_i=\frac{-D_i}{h}\left(1+\frac{\nu}{\ln\chi}\right)\left(\frac{\chi-1}{\chi-\exp(-\nu)}\right)\times\left(c_{ih}-c_{i0}\exp(-\nu)\right) \tag{12}$$

where ν, c_{i0} and c_{ih} are defined in eqn. (5) and χ is the ratio of the total ionic concentration on the donor side ($x=h$) to that on the receptor side ($x=0$):

$$\chi=\frac{\sum_i c_{ih}+\sum_k\bar{c}_{kh}}{\sum_i c_{i0}+\sum_k\bar{c}_{k0}} \tag{13}$$

Note that eqn. (12) is applicable only when the magnitude of the charge on each ion is identical. Practically, this restricts its utility for iontophoretic drug delivery to monovalent ions, since Na^+ and Cl^- are the predominant ions in the body.

The total electric current which passes through the membrane can be calculated by substituting eqn. (12) and a similar formula for negative ions into eqn. (7). The result is:

$$I=\frac{|z|F}{h}\left(\frac{\chi-1}{\ln\chi}\right)\left\{\ln(\chi/\xi)\left(\frac{V_h-\xi V_0}{\chi-\xi}\right)-\ln(\xi\chi)\left(\frac{\xi U_h-U_0}{\xi\chi-1}\right)\right\} \tag{14}$$

where U and V are defined as in eqn. (8) and

$$\xi=\exp(|\nu|)=\exp(|z|e\Delta\phi\ /kT) \tag{15}$$

Equation (14) embodies the current–voltage characteristic of the membrane, since it gives the net electrical current resulting from an applied potential $\Delta\phi$. It is in general nonlinear [5] and does not pass through the origin except in special cases. Instead, the net current is zero at some finite potential $\Delta\phi_0$, the diffusion potential defined earlier. $\Delta\phi_0$ is found implicitly as the solution to the following equations, which are obtained by setting $I=0$ in eqn. (14):

$$\left(\frac{V_h-\xi V_0}{\xi U_h-U_0}\right)=\left(\frac{\ln\chi+\ln\xi}{\ln\chi-\ln\xi}\right)\left(\frac{\chi-\xi}{\xi\chi-1}\right) \tag{16}$$

$$\Delta\phi_0=(kT/e|z|)\ln\xi \tag{17}$$

One first solves eqn. (16) for ξ, then uses this value in eqn. (17) to calculate $\Delta\phi_0$.

The nature of the nonlinearity of eqn. (14) deserves a comment. This effect occurs because different ions fill the membrane at positive and negative values of the potential drop $\Delta\phi$, as long as the composition of the electrolytes on opposite sides of the membrane is different. If these ions, furthermore, have different mobilities within the membrane, the effective membrane resistance changes with the sign of the external potential. Thus, the current–voltage characteristic of the membrane is bilinear, consisting of two straight-line portions having different slopes and joined by a smooth curve. Reference [5] has a good discussion of this phenomenon.

The flux ratio analogous to eqn. (9) for a permeant present only at $x=h$ is:

$$\frac{J(\nu)}{J(0)}=\left(1+\frac{\nu}{\ln\chi}\right)\left(\frac{\chi-1}{\chi-\exp(-\nu)}\right) \tag{18}$$

As in the constant field model, the active/passive flux ratio is calculated as $J(\nu)/J(\nu_0)$ rather than from eqn. (18). In the limit as $\chi \to 1$ (equal ionic concentrations on both sides of the membrane) the electroneutrality approximation yields the same result as the constant field approximation [7].

Transference numbers

The transference number for an ion in the membrane may be defined as the fraction of the net electrical current carried by that species*:

$$t_i = |z_i J_i F / I| \tag{19}$$

By combining the equations for individual ionic flux J_i and total current I according to eqn. (19) one can obtain an expression for the transference number for any species. The result for positive ions within the Planck approximation is:

$$t_i = (\xi D_i c_{ih} - D_i c_{i0}) \left\{ (\xi U_h - U_0) - \left(\frac{\ln \chi - \ln \xi}{\ln \chi + \ln \xi} \right) \left(\frac{\chi \xi - 1}{\chi - \xi} \right) (V_h - \xi V_0) \right\}^{-1} \tag{20}$$

For $\xi \gg 1$, i.e., an appreciable positive potential $\Delta\phi$ driving positive ions from $x=h$ to $x=0$ and negative ions from $x=0$ to $x=h$, one may neglect the back flow of ions against the potential gradient, giving:

$$t_i = \frac{D_i c_{ih}}{U_h - \chi V_0 \left(\frac{\ln \chi - \ln \xi}{\ln \chi + \ln \xi} \right)} \tag{21}$$

In the case of very large driving voltages, or when the ionic concentration ratio χ is near unity, the ratio of logarithms approaches -1 and the transference number for positive ions approaches:

$$t_i = \frac{D_i c_{ih}}{U_h + \chi V_0} \tag{22}$$

The corresponding formula for negative ions at large positive ξ is:

$$t_i = \frac{\chi D_i c_{i0}}{U_h + \chi V_0} \tag{23}$$

Equations (22) and (23) may be considered to be asymptotic transference number formulae, since they no longer depend on the driving voltage.

Since $U_h = \sum_i D_i c_{ih}$ and $V_0 = \sum_i D_i c_{i0}$, it is easy to see for the asymptotic formulae that $\sum_i t_i + \sum_h t_h = 1$.

Boundary conditions for an oil membrane

For the case of an oil (or lipid) membrane, the equations presented to this point are accurate if all concentrations and potentials are taken to be those existing *within the membrane*. In order to calculate ionic fluxes across the membrane given concentrations and potentials *external to the membrane*, the partition equilibria at the two interfaces must be considered. As discussed earlier, a general, thermodynamic way of approaching this problem is to solve simultaneously equations of the form of eqn. (3) for each ion at each interface along with the other equations of the model. The particulars of the solution depend on the numbers and types of ions present; we consider two relatively simple, but useful, cases. In this section, the boundary conditions at a single interface are developed in the framework of the Planck approximation. The combined effect of the two interfaces is considered later.

Case 1: A binary, 1:1 electrolyte at the oil–water interface

The situation is depicted in Fig. 2(a); for clarity we choose the salt to be NaCl. The relevant equations are:

$$\mu^\circ_{Na^+,s} + RT \ln [Na^+]_s + F\phi_s = \mu^\circ_{Na^+,m} + RT \ln [Na^+]_m + F\phi_m \tag{24}$$

$$\mu^\circ_{Cl^-,s} + RT \ln [Cl^-]_s - F\phi_s = \mu^\circ_{Cl^-,m} + RT \ln [Cl^-]_m - F\phi_m \tag{25}$$

$$[Na^+]_s = [Cl^-]_s = [NaCl]_s \tag{26}$$

$$[Na^+]_m = [Cl^-]_m = [NaCl]_m \tag{27}$$

By substituting eqns. (26) and (27) into eqns. (24) and (25) and then adding and subtracting the results, it can readily be shown [5] that:

$$K_{NaCl} = \frac{[NaCl]_m}{[NaCl]_s} = \exp\left(\frac{\Delta_{Na} + \Delta_{Cl}}{2RT} \right) \tag{28}$$

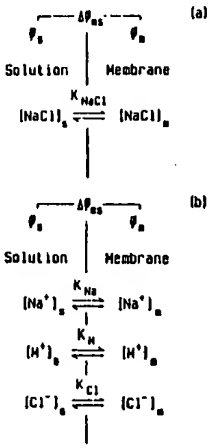

Fig. 2. Model for ionic partitioning at a membrane–solution interface. The electrochemical potential of each species is assumed to be the same on both sides of the interface. The partitioning phenomena and the potential jump $\Delta\phi_{os} = \phi_o - \phi_s$ can be quite important for the case of an oil membrane in contact with an aqueous solution. (a) The two-ion case leads to constant values of K_{NaCl} and $\Delta\phi_{os}$ — eqns. (28) and (29); (b) the three-ion case leads to concentration-dependent values of the K_i and $\Delta\phi_{os}$ — eqns. (33)–(39).

$$\Delta\phi_{os} = \phi_o - \phi_s = (\Delta_{Na} - \Delta_{Cl})/2F \tag{29}$$

where

$$\Delta_{Na} = \mu^\circ_{Na^+,s} - \mu^\circ_{Na^+,m}$$

and

$$\Delta_{Cl} = \mu^\circ_{Cl^-,s} - \mu^\circ_{Cl^-,m}$$

Thus, the phase boundary potential, $\Delta\phi_{os}$, and oil–water partition coefficient for the salt, K_{NaCl}, can be calculated from a knowledge of standard state chemical potential differences of the ions in the two phases. This solves the problem in principle; in practice, estimation or experimental determination of the thermodynamic properties is required. Note that both $\Delta\phi_{os}$ and K_{NaCl} are independent of the concentration of salt.

Case 2: a ternary, 1:1 electrolyte at the oil–water interface

The situation is depicted in Fig. 2(b). An additional cation, M^+, has been included in the problem. This may be thought of as a drug ion which is partitioning in the presence of NaCl. The equations which now describe the interfacial equilibrium are eqns. (24), (25), and (30)–(32):

$$\mu^\circ_{M^+,s} + RT \ln [M^+]_s + F\phi_s = \mu^\circ_{M^+,m} + RT \ln [M^+]_m + F\phi_m \tag{30}$$

$$[Na^+]_s + [M^+]_s = [Cl^-]_s \tag{31}$$

$$[Na^+]_m + [M^+]_m = [Cl^-]_m \tag{32}$$

The solution to these five equations is outlined in Appendix 2. The result is:

$$K_{Na} = \frac{[Na^+]_m}{[Na^+]_s} = \left(\frac{\alpha}{\beta\gamma} \right)^1 \tag{33}$$

$$K_M = \frac{[M^+]_m}{[M^+]_s} = \left(\frac{\alpha\beta^2}{\gamma} \right)^1 \tag{34}$$

$$K_{Cl} = \frac{[Cl^-]_m}{[Cl^-]_s} = \left(\frac{\alpha\gamma}{\beta} \right)^1 \tag{35}$$

*Note that according to this definition, the transference number of an individual ion can exceed unity. The vectoral sum of the transference numbers (obtained by retaining the sign of $z_i J_i$ in eqn. 19) is still unity, however.

$$\Delta\phi_m = \phi_m - \phi_s$$

$$= \frac{1}{3F}\left\{\Delta_{Na} + \Delta_M - \Delta_{Cl} + \frac{RT}{4}\ln\left(\frac{\gamma^2}{\alpha\beta^2}\right)\right\} \quad (36)$$

where the Δ_i are defined as in eqns. (28) and (29) and

$$\alpha = \exp\frac{\Delta_{Na} + \Delta_M + 2\Delta_{Cl}}{RT} \quad (37)$$

$$\beta = \exp\frac{\Delta_M - \Delta_{Na}}{RT} \quad (38)$$

$$\gamma = \left(\frac{[Na^+]_s + \beta[M^+]_s}{[Na^+]_s + [M^+]_s}\right)^2 \quad (39)$$

Note that the ionic partition coefficients and the phase boundary potential are now functions of concentration since γ is concentration dependent.

EXAMPLE: A MONOVALENT DRUG TRANSPORTED IONTOPHORETICALLY IN THE PRESENCE OF SODIUM CHLORIDE

Consider the situation shown in Fig. 1, where the electrolyte at $x=0$ is now thought of as extracellular fluid within the body and the electrolyte at $x=h$ is a donor solution containing a monovalent, cationic drug which is placed on the skin. For simplicity, the extracellular fluid will be assumed to be normal saline (0.15 M NaCl), and the diffusion coefficients of sodium and chloride ions within the membrane will be taken to be equal. These seem to be reasonable assumptions, since Na^+ and Cl^- are by far the most prevalent ions in the extracellular fluid and are relatively small and mobile as well. Furthermore, Tregear [16] has shown that the permeability of both rabbit skin and human skin to Na^+ and Br^- is comparable, and the two halogens might be expected to behave similarly*. We again consider two cases. In Case 1, the donor solution contains only the drug and chloride ion in equal concentrations; in Case 2, the donor solution contains normal saline in addition to the drug and its chloride counterion. The model presented earlier may now be used to calculate drug transport across the membrane under the electroneutrality approximation.

Case 1: No NaCl in donor side; normal saline on receptor side

Let M^+ represent a cationic drug present only on the donor side of a water membrane, and D_M be the diffusion coefficient of the drug in the membrane. The ionic concentration ratio χ for this situation is simply given by:

$$\chi = ([M^+]_h + [Cl^-]_h)/([Na^+]_0 + [Cl^-]_0)$$

$$= [M^+]_h/[Na^+]_0$$

$$= [M^+]_h/0.15\,M \quad (40)$$

since $[Cl^-]_h = [M^+]_h$ and $[Cl^-]_0 = [Na^+]_0$.

The flux relative to that with a short circuit condition across the membrane is given by eqn. (18). A plot of this relationship versus the dimensionless driving force ν is shown in Fig. 3. The flux enhancement for positive values of ν decreases as the drug concentration increases. The situation where $\chi=1$ corresponds to the constant field model; in this case the flux ratio is calculated from eqn. (9) rather than from eqn. (18).

Since the flux at zero voltage, $J(0)$, is proportional to $[M^+]_h$, the actual amount of drug transported at a given applied potential, $J(\nu)$, still increases with increasing drug concentration, despite the fact that the enhancement factor falls. A plot of the total drug flux, relative to that with $\chi=1$ and $\nu=0$, is shown in Fig. 4. The point to remember here is that $J(\nu)$ is not directly proportional to drug concentration ($[M^+]_h$), as it is under the Goldman approximation. Instead, it increases at a rate given approximately (for large values of ν) by $[M^+]_h(\chi-1)/(\chi \ln \chi)$. This is obtained by taking the limit of eqn. (18) as $\nu\to\infty$, recalling that $J(0)\propto[M^+]_h$.

Under open circuit conditions a diffusion potential $\Delta\phi_0$ develops across the membrane due to the differential mobilities of the drug, Na^+ and Cl^-. This potential is calculated from eqns. (16) and (17). A plot of $\Delta\phi_0$ for various values of D_M and $[M^+]_h$ is shown in the inset of Fig. 5. For drugs which diffuse less readily than chloride, the sign of $\Delta\phi_0$ is positive, resulting in an enhancement of drug flux relative to the short circuit condition. The enhancement, as calculated from eqns. (6) and (18), is shown in Fig. 5. Enhancement factors $J(\nu_0)/J(0)$ of about 2 are obtained for concentrated solutions of slowly diffusing drugs.

For most iontophoresis experiments, the quantity most easily compared with theory is the ratio of the flux obtained under iontophoresis versus that obtained via passive diffusion.

*Burnette and Ongpipattanakul [11] have recently shown that the transference number for Na^+ during constant-current iontophoresis through human skin from a buffered saline solution is about twice that of Cl^-. Since the mobility of Na^+ in free solution is less than that of Cl^-, this means that the skin is permselective for Na^+ versus Cl^-. This permselectivity may be due to a higher membrane diffusion coefficient for Na^+ or (as proposed in Ref. [11]) to Donnan exclusion of negative ions due to the skin's net negative charge.

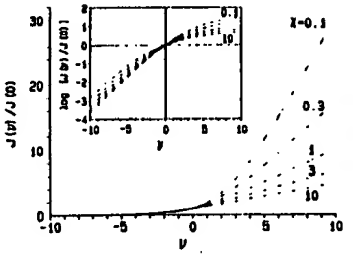

Fig. 3. Iontophoretic flux enhancement ratio for a permeant present only on one side ($x=h$) of a membrane, calculated according to eqn. (18). The parameter ν is the dimensionless driving force $z_i e\Delta\phi/kT$ (eqn. 6) and χ is the total ion concentration ratio defined in eqn. (13). The inset shows the same equation plotted on a semi-logarithmic scale.

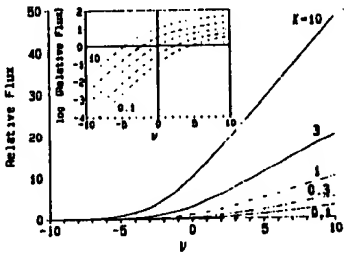

Fig. 4. Total drug flux ($J_{M,r}$) across the membrane, relative to that obtained with $\nu=0$ and $\chi=1$, for the case in which the donor solution contains only MCl and the receptor solution only NaCl. The ordinate is actually calculated as $\chi J(\nu)/J(0)$ where $\chi=[MCl]_h/0.15$ as in eqn. (40) and $J(\nu)/J(0)$ is calculated using eqn. (18). Although $J(\nu)/J(0)$ decreases with increasing χ, the total drug flux still increases, as one would expect.

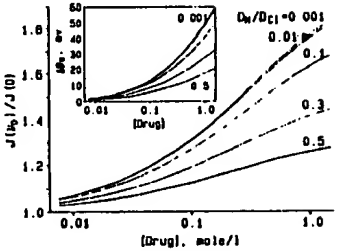

Fig. 5. Enhancement of passive diffusion flux due to development of a diffusion potential $\Delta\phi_0$ across the membrane in the absence of an applied voltage. The value of $\Delta\phi_0$ (inset) is obtained from eqns. (16) and (17), and then $J(\nu)/J(0)$ is calculated from eqns. (6) and (18). This calculation is specific for the situation described in Fig. 4, i.e., the donor phase contains only MCl and the receptor phase only NaCl.

In the present model this property is given by the ratio $J(\nu)/J(\nu_0)$, which is plotted in Fig. 6. A similar plot is obtained if the flux ratio is plotted against total current I, since the current–voltage characteristic of the membrane is bilinear. In other words, for a fixed concentration of drug in the donor phase and moderate-to-high driving voltages, drug delivery in this ideal membrane model is proportional to total current and also to the potential drop across the membrane.

Finally, we consider the drug transference number, t_M, the fraction of the total current I carried by the drug. This is a measure of the efficiency of drug delivery and becomes an important consideration when the power source is limited or when I approaches the limit of patient tolerance. In this example the asymptotic value of t_M is easily calculated from eqn. (22), which simplifies to a ratio of drug and chloride ion diffusion coefficients:

$$t_M = D_M/(D_M + D_{Cl}) \tag{41}$$

At moderate currents, slightly higher efficiencies are obtained — eqns. (20) and (21) give the precise calculations. The message here is

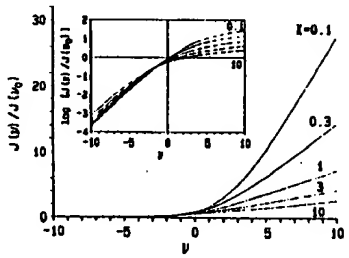

Fig. 6. Observed ratio of iontophoretic drug flux to that obtained under passive diffusion conditions for the situation described in Figs. 4 and 5. This ratio differs from that calculated in Fig. 3 in that the effect of the diffusion potential $\Delta\phi_0$ is now properly taken into account. This is the observable flux ratio in most iontophoresis experiments (if transport of the neutral species can be neglected).

that the efficiency of drug delivery is largely determined by the ratio of drug diffusivity in the skin to that of the predominant counterion on the opposite side of the membrane. It is independent of drug concentration in this example.

Now suppose that the membrane has an oily or lipoidal nature rather than being simply an immobilized aqueous phase. At each interface a salt partition coefficient and a phase boundary potential of the form of eqns. (28) and (29) must be considered. At $x=0$, the salt is NaCl; at $x=h$, MCl. We consider the effect of the oil phase on the flux of M^+ across the membrane at some applied potential $\Delta\phi$. In the absence of partitioning effects that flux can be calculated from eqn. (18) with $\nu = e\Delta\phi/kT$, $\chi = [MCl]_{o,h}/[NaCl]_{o,0}$, and $J(0) = (D_M/h)[MCl]_{o,h}$ (J_{M^+} is identified with $J(\nu)$). When oil–water partitioning is considered, eqn. (18) is still valid (since the transport process within the membrane is unchanged), but ν, χ, and $J(0)$ must be calculated differently to reflect the new boundary conditions. Applying eqns. (28) and (29) at both interfaces one obtains:

$$\nu = \frac{e}{kT}\left[\Delta\phi - \frac{1}{2F}(\Delta_{Na} - \Delta_M)\right] \tag{42}$$

$$\chi = \frac{[MCl]_{o,h}}{[NaCl]_{o,0}} \exp\frac{|\Delta_M - \Delta_{Na}|}{RT} \tag{43}$$

$$J(0) = \frac{D_M}{h} K_{MCl}[MCl]_{o,h} = \frac{D_M}{h}[MCl]_{o,h} \exp\left(\frac{\Delta_M + \Delta_{Cl}}{2RT}\right) \tag{44}$$

These formulae are expected to apply as long as the system is not driven so hard that the equilibria represented by eqns. (24), (25) and (30) are not established.

In general, oil–water partition coefficients for ions are small, which implies that the standard state chemical potential differences Δ_i are all large and negative. Thus, eqn. (44) shows that the flux of M^+ (and other ionic fluxes) is greatly reduced by unfavorable partitioning compared to that expected for aqueous membranes. The exact magnitude of the effect is sensitive to the relative partitioning properties of M^+ and Na^+, as shown by eqns. (42) and (43).

Case 2: Normal saline in both donor and receptor phases

We now consider the case where the drug and its (chloride) counterion are added to a donor phase having the same initial composition as the receptor phase. In this case the ionic concentration ratio χ simplifies to:

$$\chi = ([M^+]_h + [Na^+]_h)/[Na^+]_0 = ([M^+]_h + 0.15)/0.15 \tag{45}$$

where $[M^+]_h$ is the drug concentration as before. The flux enhancement ratio $J(\nu)/J(0)$ is calculated exactly as in the previous example (Fig. 3), except that χ now has a different relationship to drug concentration. The diffusion potential $\Delta\phi_0$ and the flux enhancement ratio $J(\nu_0)/J(0)$ are somewhat lower than before, due to the presence of the additional electrolyte in the donor phase. A comparison is shown in Table 1.

The drug transference number t_M is now a

TABLE 1

Diffusion potential $\Delta\phi_0$ and flux enhancement ratio $J(\nu_0)/J(0)$ for different concentrations of a permeant M^+ in the presence and absence of NaCl on the donor side of a homogeneous membrane. Normal saline is present on the receptor side, the counterion of M^+ is Cl^-, and the relative diffusion constants have been taken to be $D_{Na} = D_{Cl} = 10\,D_M$. The results are calculated from eqns. (16)–(18), with χ defined by either eqn. (40) (no NaCl on donor side) or eqn. (45) (0.15 M NaCl on donor side).

$[M^+]$ (M)	No NaCl		0.15 M NaCl	
	$\Delta\phi_0$ (mV)	$J(\nu_0)/J(0)$	$\Delta\phi_0$ (mV)	$J(\nu_0)/J(0)$
0.01	2.3	1.07	0.7	1.01
0.03	5.1	1.14	2.1	1.04
0.1	11.6	1.27	6.4	1.12
0.3	22.5	1.44	15.8	1.28
1.0	41.0	1.63	34.6	1.51

strong function of concentration, since the drug competes with Na^+ on the donor side as well as with Cl^- on the receptor side as the current-carrying species. Under the assumption that D_{Na} and D_{Cl} in the membrane are identical (as in the previous example), the asymptotic value of t_M calculated from eqn. (22) may be written as:

$$t_M = \frac{D_M}{D_M + D_{Cl}(1 + 0.30/[M^+]_h)} \tag{46}$$

A plot of this relationship is shown in Fig. 7. Efficient drug delivery is possible only if the drug concentration is kept high and the value of the drug diffusivity D_M is not too low. From the efficiency standpoint, Case 1 is much preferred to Case 2.

We now consider the effect of an oil membrane on the flux of M^+. As in the previous example, eqn. (18) is still a valid way to calculate $J(\nu)$ (i.e., J_{M^+}) provided ν, χ, and $J(0)$ are computed appropriately. In this case, the three ion partition coefficients and phase boundary potentials given in eqns. (33)–(36) must be computed at each interface in order to deter-

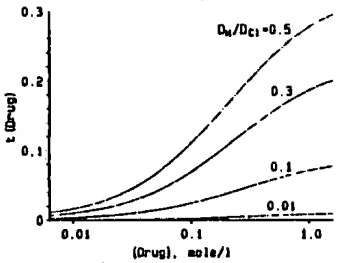

Fig. 7. Asymptotic transference number of a drug undergoing iontophoretic transport through a membrane, calculated from eqn. (46). In this case, normal saline (0.15 M) is assumed to be present on both sides of the membrane and the concentration of drug in the donor phase is allowed to vary. Efficient drug delivery is obtained only when the drug concentration is reasonably high and its diffusivity is not too low compared with that of sodium and chloride ions.

mine the boundary conditions at the membrane surfaces. The results of this calculation are:

$$\nu = e/\phi\ /kT + \tfrac{1}{2}\ln(\gamma_{s=h}/\gamma_{s=0}) \quad (47)$$
$$= e/\phi\ /kT + \tfrac{1}{2}\ln\gamma_{s=h}$$

$$\chi = \{[M^+]_{s,h}K_{M,h} + [Na^+]_{s,h}K_{Na,h} + [Cl^-]_{s,h}K_{Cl,h}\}\{[M^+]_{s,0}K_{M,0} + [Na^+]_{s,0}K_{Na,0} + [Cl^-]_{s,0}K_{Cl,0}\}^{-1}$$
$$= \{([M^+]_{s,h}\beta^\nu + [Na^+]_{s,h})/\gamma_{s=h} + ([M^+]_{s,h} + [Na^+]_{s,h})\gamma_{s=h}\}\{[NaCl]_{s,0}\}^{-1} \quad (48)$$

$$J(0) = \frac{D_M}{h}\{K_{M,h}[M^+]_{s,h} - K_{M,0}[M^+]_{s,0}\} = \frac{D_M}{h}[M^+]_{s,h}\left(\frac{\alpha\beta^\nu}{\gamma_{s=h}}\right)^{\frac{1}{2}} \quad (49)$$

where the final simplification in each case results from the fact that $[M^+]_{s,0}=0$ in this example.

In eqns. (47)–(49), α, β, and γ are the quantities defined in eqns. (37)–(39) and the ionic concentrations are those existing in the solution exterior to the membrane. As in the two-ion case, the major effect is a reduction in the net flux through a reduction in $J(0)$, since $K_{M,h} \ll 1$.

DISCUSSION

Despite the complexity which quickly arises when electrodiffusion through membranes is analyzed quantitatively, some basic principles emerge from such an analysis which provide useful guidelines for thinking about iontophoresis experiments. These include:

(1) If the skin behaves as an ideal membrane, iontophoretic drug flux will be essentially proportional to the total electrical current and also to the voltage drop across the skin. Under constant voltage conditions, drug flux increases with increasing drug concentration in the donor solution ($[M^+]_h$) at a rate given approximately by $[M^+]_h(\chi-1)/(\chi\ln\chi)$ where χ is defined in eqn. (13).

(2) The observable quantity $J(\nu)/J(\nu_0)$, the active to passive flux ratio of drug across the skin, is somewhat reduced from the theoretical ratio $J(\nu)/J(0)$ given in eqn. (18), owing to the fact that the (presumably) slower diffusion of drug across the skin relative to its counterion gives rise to a diffusion potential which helps drive the drug across the skin in the absence of an applied voltage.

If the flux from passive diffusion includes a significant component from transport of the nonionized form of the drug, the observed ratio $J(\nu)/J(\nu_0)$ will be still lower, since the transport of neutral drug will not be susceptible to direct electrostatic enhancement.

(3) The efficiency of drug delivery (i.e., the drug transference number t_M) can be maximized by minimizing the number of small, mobile ions in the donor solution having the same charge as the drug. For a positively charged drug this would mean minimizing or eliminating ions like Na^+ and K^+ in the donor solution. The use of bulky organic ions or the drug itself to buffer the solution pH should be considered.

The theoretical limit for the drug transference number is given by a ratio which depends on the drug diffusion coefficient in the membrane and that of the predominant counterion on the other side of the skin (eqn. 41). Treatments which differentially alter these diffusion coefficients could increase the efficiency of drug delivery. For example, a treatment which lowers the size dependence of membrane diffusion coefficients (perhaps an adjuvant which fluidizes the membrane) might enhance the transport of large drug ions relative to Na^+ and Cl^-.

(4) Low membrane-water partition coefficients for ionic species significantly retard the iontophoretic transport of drugs through lipid pathways in the skin compared with transport through aqueous pathways. This has been confirmed experimentally by studies of iontophoretic transfer of dyes into the skin [10,17,18]. We have presented equations, e.g. eqns. (33)–(39), which give the form of ionic partitioning at a lipid–water interface in the equilibrium or near-equilibrium limit. The partition coefficients are concentration dependent, except in the simplest cases. Practical application of these equations involves estimation of the standard state chemical potentials of ions in aqueous solutions and in the skin lipid matrix.

It has been known for some time that the skin may possess a net negative charge depending on pH [19]. This net charge has been invoked to explain the electroosmotic transport of water across mouse skin [9,12] and the iontophoretically induced transport of thyrotropin releasing hormone into hairless mouse skin at a pH near its pI value [10]. Recently, Burnette and Ongipipattanakul [11] have demonstrated a similar phenomenon using [^{3}H]mannitol as the test permeant. The present theory does not account for these effects, which apparently arise from a combination of a fixed negative charge on the skin and a significant coupling between solute and solvent transport through the skin. The permselectivity of human skin for Na^+ over Cl^- demonstrated by the latter investigators is further evidence for the importance of the skin's negative charge to iontophoretic transport.

A fixed charge density in the membrane can readily be incorporated into the present theory by including an extra term in the electroneutrality condition, eqn. (11). Fixed charges may markedly alter ionic transport through the membrane, owing to the Donnan exclusion conditions which pertain at each interface [5]. Unfortunately for the analytically minded, the inclusion of fixed charges into the problem causes the integration outlined in Appendix 1 to break down, forcing one to more and more complex equations or to numerical integration techniques. Nevertheless, a considerable amount is known about such systems [5,20]. Considering the experimental evidence for a significant negative charge on skin, the extension of the present theory to include charged membranes appears to be worthwhile.

In order to explain electro-osmotic effects or the enhancement of neutral molecule flux, another level of complexity must be added to the model. The most general way of doing this is by adding solute–solvent coupling terms in the context of irreversible thermodynamics [20–22]. Since this is a phenomenological approach, a considerable amount of experimental information regarding solute and solvent permeabilities, osmotic pressure, and the like must be obtained in order to unambiguously define the system. Such an effort may be worthwhile if neutral molecule flux enhancement proves to be of practical importance. The writers' opinion, however, is that this effect is of secondary importance compared to the electrostatic enhancement of ionic fluxes.

An even more serious concern with the model presented here is the apparent inability to predict ionic flux enhancements or membrane current–voltage characteristics at the moderate-to-high current levels of practical importance to drug delivery. Experimental work in our own laboratory [13] and one other [23] has shown that the electrical resistance of the skin drops markedly under such conditions, resulting in ionic flux enhancements considerably larger than predicted by the homogeneous membrane theory. The effect is partially, although not completely, reversible [24]. An interesting corollary to this effect is that ionic transference numbers within the skin appear to be preserved [11,13]. It seems unlikely that a minor extension of the present theory (to include, for example, fixed charge, polyvalent electrolytes, or a multilaminate membrane structure) will explain these effects.

We propose that at least two important phenomena occur in skin under moderate-to-high iontophoretic currents which are not accounted for by the present model: (1) Local heating produces a partial breakdown of membrane resistance to electrical and mass transport. To effect this, most of the power dissipation must be confined to a very small volume within the skin (perhaps the epithelial cell membranes lining the appendageal pathways through the skin).

The effects of this electrical breakdown would be expected to be irreversible. (2) Thermodynamic equilibrium is not maintained at the lipid-water interfaces within the skin. For a multilaminate structure such as skin, a number of such interfaces may be present. Nonequilibrium interfacial phenomena could well result in a drop in electrical resistance at high power levels which reverses when the power is turned off. The writers are presently investigating a kinetic model based on the theory of heterogeneous reactions which may accommodate the observed effects [25].

CONCLUSIONS

Ionic mass transport through a homogeneous membrane has been analyzed under a mathematical approximation (electroneutrality assumption) which appears to be appropriate for describing drug transport through skin. Experimental departures from this theory are very likely to represent deviations from ideal behavior of the skin itself and thus, may be used to develop physical models for skin which more accurately reflect the observed behavior. The present model has the advantage of allowing quantitative predictions of iontophoretic transport through skin from estimates of ionic diffusion coefficients and membrane-water partition coefficients.

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APPENDIX 1

Solution of the Nernst–Planck flux equations for 1:1 electrolytes under the electroneutrality approximation

The system of equations to be solved is:

$$J_i = -D_i \mathrm{d}c_i/\mathrm{d}x + D_i z_i e E c_i/kT \qquad i=1, M \tag{A-1}$$

$$J_k = -D_k \mathrm{d}c_k/\mathrm{d}x + D_k z_k e E c_k/kT \qquad k=1, N \tag{A-2}$$

$$\sum_{i=1}^{M} z_i c_i(x) + \sum_{k=1}^{N} z_k c_k(x) = 0 \tag{A-3}$$

where the subscript i refers to positive ions, k to negative ions, and the boundary conditions are those shown in Fig. 1. For the case of 1:1 electrolytes, $z_i = -z_k = |z|$ for all i and k. In this case, dividing eqns. (A-1) by D_i and (A-2) by D_k and summing them yields:

$$j^+ = \sum_i J_i/D_i + \sum_k J_k/D_k = -\mathrm{d}[C(x)]/\mathrm{d}x \tag{A-4}$$

where $C(x) = \sum_i c_i + \sum_k c_k$ is the total ionic concentration, and the second term on the right has dropped out due to eqn. (A-3). Thus $C(x)$ must be a linear function of x in the membrane. Application of the boundary conditions at $x=0$ and $x=h$ gives:

$$C(x) = (C_h - C_0)x/h + C_0 \tag{A-5}$$

Next, one divides eqns. (A-1) by D_i and (A-2) by D_k and subtracts (A-2) from (A-1). The other term on the right drops out, leaving:

$$j^- = iJi/Di - kJk/Dk = (|z|eE/kT)C(x) \tag{A-6}$$

Equation (A-6) can be satisfied for all x if and only if E is proportional to $C(x)^{-1}$. Assuming this form, integrating to obtain $\phi = -\int E\mathrm{d}x$, and applying the boundary conditions on ϕ yields:

$$\phi(x) = \frac{\Delta\phi \ln\,[1+(\chi-1)x/h]}{\ln \chi} \tag{A-7}$$

and

$$E(x) = \frac{-\Delta\phi}{h \ln \chi} \frac{\chi-1}{[1+(\chi-1)x/h]} \tag{A-8}$$

where $\chi = C_h/C_0$ is the ratio of the total ionic concentrations on opposite sides of the membrane. Substitution of eqn. (A-8) into eqns. (A-1) and (A-2) leads to a linear, first-order differential equation of the form $\mathrm{d}c_i/\mathrm{d}x + P(x)c_i = Q$, where $P(x) = -z_i eE(x)/kT$ and $Q = -J_i/D_i$. This equation may be directly integrated after multiplication by the integrating factor $\exp\int P(x)\mathrm{d}x$. Application of the boundary conditions on the c_i and c_k then leads to eqn. (12) in the text. The solution for negative ions is the same as that for positive ions if the sign of the charge z_i or z_k is included in the definition of $\nu = z_i e\Delta\phi/kT$.

APPENDIX 2

Partitioning of three monovalent ions at an oil–water interface

We consider the situation depicted in Fig. 2. Three ions — Na^+, M^+, and Cl^- — are in equi-

librium at a membrane–solution (oil–water) interface. Within the context of the electroneutrality approximation, the conditions of electrochemical equilibrium are as follows:

$$\mu^{\circ}_{Na^+,s} + RT \ln [Na^+]_s + F\phi_s = \mu^{\circ}_{Na^+,m} + RT \ln [Na^+]_m + F\phi_m \quad \text{(B-1)}$$

$$\mu^{\circ}_{Cl^-,s} + RT \ln [Cl^-]_s - F\phi_s = \mu^{\circ}_{Cl^-,m} + RT \ln [Cl^-]_m - F\phi_m \quad \text{(B-2)}$$

$$\mu^{\circ}_{M^+,s} + RT \ln [M^+]_s + F\phi_s = \mu^{\circ}_{M^+,m} + RT \ln [M^+]_m + F\phi_m \quad \text{(B-3)}$$

$$[Na^+]_s + [M^+]_s = [Cl^-]_s \quad \text{(B-4)}$$

$$[Na^+]_m + [M^+]_m = [Cl^-]_m \quad \text{(B-5)}$$

In eqns. (B-1)–(B-5), s refers to the solution phase, m to the membrane phase, the μ_i° are standard state chemical potentials, ϕ is the electrical potential, and F is the Faraday constant. We assume that the solution concentrations and potential are known to the investigator and that the μ_i°, or their differences, $\Delta_i = \mu^{\circ}_{i,s} - \mu^{\circ}_{i,m}$, have been previously determined. The objective, therefore, is to determine the four unknown quantities $[Na^+]_m$, $[Cl^-]_m$, $[M^+]_m$, and ϕ_m given eqns. (B-1)–(B-5). Note that there are actually four equations and four unknowns, since (B-4) does not contain an unknown quantity.

We begin by making four new linear combination of (B-1)–(B-5). They are:

Equations (B-1) − (B-2) + (B-3):

$$\Delta\phi_{ms} \equiv \phi_m - \phi_s = \frac{1}{3F}\left\{\Delta_{Na} + \Delta_M - \Delta_{Cl} + RT \ln \frac{[Na^+]_s[M^+]_s[Cl^-]_m}{[Na^+]_m[M^+]_m[Cl^-]_s}\right\} \quad \text{(B-6)}$$

Equations (B-1) + 2 × (B-2) + (B-3), followed by exponentiation:

$$\alpha \equiv \exp\left(\frac{\Delta_{Na} + \Delta_M + 2\Delta_{Cl}}{RT}\right) = \frac{[Na^+]_m[M^+]_m[Cl^-]_m^2}{[Na^+]_s[M^+]_s[Cl^-]_s^2} \quad \text{(B-7)}$$

Equations (B-3) − (B-1), followed by exponentiation:

$$\beta \equiv \exp\left(\frac{\Delta_M - \Delta_{Na}}{RT}\right) = \frac{[Na^+]_s[M^+]_m}{[Na^+]_m[M^+]_s} \quad \text{(B-8)}$$

Equations (B-5) ÷ (B-4):

$$K_{Cl} \equiv \frac{[Cl^-]_m}{[Cl^-]_s} = \frac{[Na^+]_m + [M^+]_m}{[Na^+]_s + [M^+]_s} \quad \text{(B-9)}$$

Substitution of eqn. (B-9) into (B-7) yields a pair of equations, (B-7)′ and (B-8), which contain only the unknowns $[Na^+]_m$ and $[M^+]_m$. These can be solved simultaneously to yield these quantities or, alternatively, the ratios $K_{Na} = [Na^+]_m/[Na^+]_s$ and $K_M = [M^+]_m/[M^+]_s$. Substitution of these results into eqn. (B-9) and then (B-6) leads directly to eqns. (33)–(39) in the text.

Patent
Attorney's Docket No. 000951-089

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Joseph B. PHIPPS	)	Group Art Unit: 3734
	)	
Application No.: 08/463,904	)	Examiner: M. Bockelman
	)	
Filed: June 5, 1995	)	
	)	
For: METHOD AND DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL	)	

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Joseph Bradley Phipps, hereby declare that:

1. I am a citizen of the United States of America residing in Maple Grove, Minnesota.

2. I received my undergraduate degree in Materials Science from University of Utah and my doctorate in Materials Science from Northwestern University.

3. I have been employed by Alza Corporation since 1991 and my current title is Director of Research, E-Trans Technology and my responsibilities include performing research in materials science and electrotransport devices, particularly waveform parameters such as voltage, current and timing to enhance biocompatibility and drug flux.

4. I am the inventor of the above-identified patent application and the Declarant of the Declaration previously submitted in the present application. I have reviewed the Official Action dated April 2, 1998, and I am familiar with the prior art cited in the Action which includes two U.S. patents identifying me as a co-inventor.

5. The Examiner's statements in the Official Action misinterpret the teachings of the prior art and several of the points which I made in my previous Declaration and are technically incorrect concerning certain aspects. In particular, the Examiner questions why I did not address the one sentence statement found in one of my previous patents, namely U.S. Patent No. 5,125,894, and instead discussed the Padmanabhan article that is referenced in the patent. The simple answer to this question is that the statement in the '894 patent is based on the Padmanabhan article and rather than discuss the statement through the '894 patent, I believed that it was proper to discuss the source of the statement and explain the reasons why the article did not teach my invention.

Nonetheless, to address the Examiner's concern that I did not expressly discuss the '894 patent, I note that the Examiner correctly points out that the '894 patent discloses the concept that a threshold concentration exists, below which the flux becomes concentration dependent, and that this threshold will likely be dependent on the physical/chemical properties of the transported species and tissues. This statement requires no unique knowledge of drug transport and is an entirely obvious concept. That is, since drug flux was known to be independent of drug concentration over some concentration range (e.g., as stated in the Padmanabhan article), and since drug flux is obviously zero at zero

concentration, then to conclude in the '894 patent that a "threshold value" exists is an obvious concept requiring no unique knowledge about the mechanism of drug transport through the tissue. In addition, the statement in the '894 patent that this threshold value is likely dependent on the physical/chemical properties of the drug species and tissues is also an obvious general principle which is devoid of mechanistic or drug-specific knowledge.

It is clear that the '894 patent is completely silent on the magnitude of the threshold value and on what physical/chemical properties of the drug molecule or tissues might influence the threshold value. Instead the '894 patent cites the Padmanabhan article as supportive of the general principles presented. In the Padmanabhan article, the range of concentration over which the flux of hydromorphone is constant is shown to be very broad and to extend to a very low value of less than 1 mM (ie, less than about 0.5 mg/ml hydromorphone). The Padmanabhan article notes that the transport number of hydromorphone in solution was greater than the transport number through the skin, and concludes:

> Therefore, the hydromorphone concentration at the skin will be greater than the bulk solution value during iontophoresis. This phenomenon may be responsible for the **lack of dependence of the transdermal delivery rate on the bulk solution concentration.** (emphasis added at page 130)

In other words, due to the mobility of the ions in the solution, the rate limiting feature is the transport through the skin and not the concentration in the donor reservoir. It would be understood by those in the art that this phenomenon is not limited to hydromorphone and would be applicable to other drugs. Accordingly, from this statement

and others in the article, it is clear that the concern for the effect of a threshold value on system performance would be diminished, not enhanced by the Padmanabhan article, which represents the depth of understanding at the time of the present invention. In contrast, my discovery that fentanyl and sufentanil have high threshold concentrations could not have been predicted from any statement made in the Padmanabhan article or, for that matter, in the '894 patent. Further proving this point is the fact that Table 2 in column 37 of the '894 patent shows that even at 10 millimolar concentration, hydromorphone exhibits a delivery rate that is comparable to much higher concentrations which supports the statement in the Padmanabhan article that I referred to in my previous Declaration that the delivery of hydromorphone was not influenced by donor solution concentration until the concentration dropped to about one millimolar which is well below the level of my invention.

While secondary to my primary disagreement with the Examiner on what is obvious and what is not, the Examiner has seemingly failed to appreciate the role of extraneous ions on the threshold concentration concept. This misinterpretation is understandable since many researchers in this field to this day fail to grasp the finer elements of the competing ion effect.

The Examiner incorrectly asserts that; (a) the presence of extraneous ions like Na^+ and K^+ in a formulation diminishes the relevance of the Kasting model cited in my previous Declaration; and, (b) that the reason that a higher threshold is observed for some drugs may be due to the extraneous ion concentrations in the formulation employed.

In making these assertions, the Examiner is assuming that the extraneous ions, if present at the beginning of treatment are still present at the end of treatment. In fact, because small excipient ions (like Na^+ and K^+) are much more mobile in the solution and skin than the fentanyl ions and are typically present in an amount less than the amount of the drug ions, they are substantially depleted during the first part of treatment. Therefore the Kasting model is an important and fully appropriate consideration of the state of the art at the time of my invention. Contrary to the Examiner's assertions, the Kasting model teaches away from my invention, even when extraneous ions are initially present, since it predicts in theory that no threshold in concentration should exist, that is, that the flux of drug at constant current should remain essentially constant until the last molecule is delivered.

The Padmanabhan article largely confirms the theory by proving that the flux of hydromorphone is independent of concentration over a broad range extending to a small drug concentration of less than 1 mM. It is therefore not proper for the Examiner to discount the importance of the Kasting model and the Padmanabhan teachings in defining the state of the art at the time of my invention.

With respect to the rejection based on Haak et al, U.S. Patent No. 5,203,768, I could not find sufficient information concerning the examples to determine the concentration of fentanyl at the end of use. However, Haak et al does not diminish the value of my discovery. The invention does not seek to define the initial concentration of the drug in the donor reservoir, but rather to limit the allowable magnitude of the final

concentration after the system has completed its period of operation. The patent clearly provides insufficient information about the formulation, system geometry, operating current, and maximum duration of operation to estimate the concentration of fentanyl in the formulation after use of the system. More importantly, Haak et al is completely silent on the issue addressed by my invention, namely, the maintenance of drug flux throughout the treatment period intended for the system. This important consideration for developing an optimal system is clearly unappreciated by Haak et al.

The Examiner's combination of Haak et al with the '894 patent would also not result in my invention. As noted above, a proper understanding of what the '894 patent teaches would lead those in the art to using a low concentration of fentanyl salt in view of the teaching that steady state delivery can be obtained at very low concentrations and in light of the potency of fentanyl. It is entirely unexpected that I have found that a very high concentration of fentanyl salt is necessary in order to obtain the iontophoretic flux defined in the claims.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 3, 1998
Date

Joseph B. Phipps